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(19) (CA) **CANADIAN PATENT** (12)

(54) Process for the Manufacture of Pharmaceutical Compositions Containing Unilamellar Liposomes

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Abstract

Process for the manufacture of pharmaceutical compositions containing unilamellar liposomes

The present invention relates to a process for the maunfacture of pharmaceutical compositions in the form of aqueous dispersions containing unilammellar liposomes comprising (I) an amphiphatic compound having biological activity and (II) a phospholipid or an analogous lipid and, optionally, an additional lipid. The liposome dispersion is obtained by preparing a homogenous mixture of the components and by dispersing the homogenous mixture in an aqueous phase. The unilamellar liposomes can be used therapeutically as carriers of amphiphatic pharmaceuticals of extremely varied kinds.

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Process for the manufacture of pharmaceutical compositions containing unilamellar liposomes

The present invention relates to a novel, advantageous process for the manufacture of pharmaceutical compositions containing unilamellar liposomes and to the use of the pharmaceutical compositions obtainable according to the process.

Liposomes have been described in the literature in numerous publications. Many investigations are concerned with their structure and use. A distinction is made between unilamellar liposomes having a double layer of lipids and multilamellar liposomes having several double layers of lipids arranged in an onion skin-like manner.

Unilamellar liposomes have a diameter of approximately from 2.0×10^{-8} to 5.0×10^{-6}m, preferably approximately from 2.0×10^{-8} to 3.0×10^{-6}m. The spherical shell consists of a double layer of lipid components, for example amphiphatic lipids, for example phospholipids, for example lecithin, cephalin or phosphatidic acid, and, optionally, neutral lipids, for example cholesterol. This double layer surrounds an

interior space which contains an aqueous phase with a compound to be encapsulated, it being possible for the compound to be encapsulated to be present in the aqueous phase and/or in the double layer, depending upon the structure of the compound and other parameters, such as temperature or concentration.

There is a great deal of interest in the therapeutic use of liposomes as carriers for active ingredients of widely varied kinds. Accordingly, liposomes have been proposed as carriers for proteins, for example antibodies or enzymes, hormones, vitamins or genes or, for analytical purposes, as carriers for labelled compounds. An example that may be mentioned is US Patent Specification No. 3 993 754 which relates to a chemotherapeutic process in the treatment of tumour cells using liposomes as carriers.

Small unilamellar liposomes (SUL) having a diameter of approximately from 2.0×10^{-8} to 1.0×10^{-7}m are especially suitable for transportation through barriers in the organism that are impermeable to large liposomes, for example through "windows" in fenestrated capillaries, lymph node tissue and interstitial spaces of various tissues.

The active ingredient in question is encapsulated either during the formation of the liposomes or subsequently by diffusion. The preparation of liposomes and the encapsulation of the active ingredients can be effected by various methods and are described in a synoptical article by Kaye, St. B., Cancer Treatment Reviews (1981), 8, 27-50. Further methods of preparing liposomes for the purpose of encapsulating active ingredients are also described by Barenholz et al., in Biochemistry, Vol. 16, No. 12, 2806-2810, and also in German Offenlegungsschriften (DOS) 28 19 855, 29 02 672, 25 32 319 and 28 42 608, in US

Patent Specification 4 053 585, and in European Patent Application 36 676.

According to the processes known hitherto, the lipid components, for example phospholipids, for example phosphatidic acid, lecithin or cephalin, and, optionally, neutral lipids, for example cholesterol, are dissolved in an organic solvent, for example chloroform or benzene. After concentration by evaporation there remains a homogeneous layer, for example a film layer, of the particular lipid components. The lipid components are subsequently dispersed in an aqueous phase which contains the particular active ingredient, for example by shaking. Unilamellar liposomes which encapsulate the active ingredient are formed in subsequent treatment with ultrasound.

European Patent Application 88 046 describes a process for the manufacture of unilamellar liposomes in which an aqueous dispersion comprising two different lipids, for example egg phosphatidic acid and lecithin, and an active ingredient, for example a muramyl peptide, is prepared and a lipid component, for example the phosphatidic acid, is converted into the ionic or dissociated form by altering the pH value of the aqueous phase.

In the synoptical work "Liposome Technology", CRC Press 1983, edited by G. Gegoriadis, in Volume II, Chapter 4, there are described aqueous liposome dispersions which contain 8-aminoquinoline derivatives. The preparation is carried out by dissolving a phospholipid, for example dipalmitoyl- or dimyristoyl-phosphatidyl choline in an organic solvent, for example chloroform, manufacturing a lipid film and dispersing this lipid film in an aqueous phase that contains the active ingredient, for example primaquine. A dis-

advantage is the permeability of these liposomes which is mentioned on page 64 of this publication and which causes losses of encapsulated active ingredient.

The problem underlying the present invention is to provide an advantageous and generally applicable process for the manufacture of pharmaceutical compositions having adequate stability and a high proportion of encapsulated active ingredient and unilamellar liposomes.

This problem is solved by the present invention which relates to a process for the manufacture of pharmaceutical compositions in the form of aqueous dispersions containing unilamellar liposomes comprising (I) an amphiphatic compound having biological activity and (II) a phospholipid or an analogous lipid and, optionally, an additional lipid.

The process according to the invention is characterised in that (I) the amphiphatic compound having biological activity and (II) the phospholipid or the analogous lipid and, optionally, the additional lipid are homogeneously mixed and the resulting homogeneous mixture is dispersed in an aqueous phase and, if necessary, the resulting aqueous dispersion is neutralised and, if desired, the resulting unilamellar liposomes are enriched and/or separated off.

In the context of the description of the present invention, the general terms employed hereinbefore and hereinafter preferably have the following meanings:

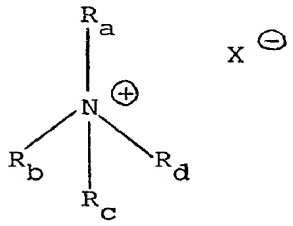
The term "lower" used in connection with organic radicals, for example lower alkyl, lower alkylene, lower alkoxy, lower alkanoyl, etc., means that such organic radicals, unless expressly defined otherwise, contain up to and including 7, preferably up to and including 4, carbon atoms.

Unless indicated otherwise, the generic names

proposed by the World Health Organisation (WHO) (Recommended International Non-proprietary Names) are used for the active ingredients, which names have been taken from the standard work "Pharmazeutische Chemie" (E. Schröder, C. Rufer and R. Schmiechen, Thieme Verlag Stuttgart, 1982) and the Merck Index (Tenth Edition).

An amphiphatic compound (I) having biological activity that is homogeneously mixed with a phospholipid (II) or an analogous lipid and, optionally, an additional lipid, can be used especially as a medicament and can be classed, for example,

as a substituted ammonium compound of the formula



(1)

in which

a) R_a represents a hydrophobic group, and R_b, R_c and R_d, independently of one another, each represents hydrogen, C_1-C_4-alkyl, 2-hydroxyethyl, allyl or cyclo-C_3-C_6-alkyl-C_1-C_3-alkyl, or two of the radicals R_b, R_c and R_d together represent C_4- or C_5-alkylene optionally interrupted by -HN-, -N(C_1-C_4-alkyl)-, -N(2-hydroxyethyl)- or by oxygen, or

b) R_a and R_b are two hydrophobic groups or together represent a hydrophobic group, and R_c and R_d, independently of one another, each represents hydrogen, C_1-C_4-alkyl, allyl or cyclo-C_3-C_6-alkyl-C_1-C_3-alkyl, or

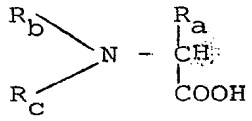
c) R_a, R_b and R_c together represent a hydrophobic group, and R_d represents hydrogen or C_1-C_4-alkyl, and $X^{\ominus}$ represents the anion of a pharmaceutically acceptable acid,

as a carboxylic acid salt of the formula

$$R_a\text{-}COO^{\ominus}\ Y^{\oplus} \qquad (2)$$

in which R_a represents a hydrophobic group, and $Y^{\oplus}$ represents the cation of a pharmaceutically acceptable base,

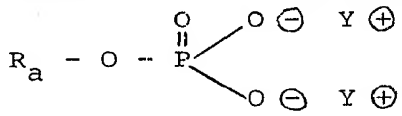
as an α-amino acid compound of the formula



(3)

in which R_a represents a hydrophobic group, and R_b and R_c, independently of one another, each represents hydrogen or C_1-C_4-alkyl,

as a phosphoric acid monoester of the formula



(4)

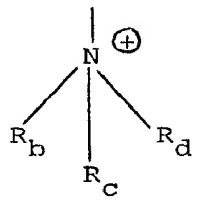
in which R_a represents a hydrophobic group and $Y^{\oplus}$ represents the cation of a pharmaceutically acceptable

base, or

as an acid addition salt of a compound having a hydrophobic group R_a and an imidazoline, imidazolidine or hydrazino group as hydrophilic group.

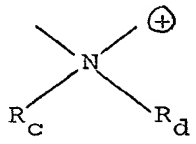
In a substituted ammonium compound of the formula 1 that can be used as a medicament, in case a) the hydrophobic group R_a is an aliphatic hydrocarbon radical that can be interrupted by an oxygen or sulphur atom, may contain the groups -C(=O)-, -O-C(=O)-, -C(=O)-NH-, -O-C(=O)-NH- or hydroxy, and can be substituted by from 1 to 3 optionally substituted, monocyclic, aliphatic or aromatic hydrocarbon radicals, by an optionally substituted, bi- or tri-cyclic, aromatic or partially saturated hydrocarbon radical, by an optionally substituted, monocyclic, aromatic, partially saturated or saturated heterocycle or by an optionally substituted, bi- or tri-cyclic, aromatic, partially saturated or benzo-fused heterocycle.

The hydrophobic group R_a can also be an optionally substituted, monocyclic, aliphatic or aromatic hydrocarbon radical or a bicyclic, aliphatic or benzo-fused hydrocarbon radical. The hydrophilic group is, for example, a group of the formula



in which R_b, R_c and R_d, independently of one another, each represents hydrogen, C_1-C_4-alkyl, for example methyl, ethyl, isopropyl or n-propyl, or 2-hydroxyethyl, or in which two of the radicals R_b, R_c and R_d together represent piperidino, piperazinyl, 1-methylpiperazinyl, 1-(2-hydroxyethyl)-piperazinyl or morpholino, and the other radical represents hydrogen.

In a substituted ammonium compound of the formula 1 that can be used as a medicament, in case b) R_a and R_b are two hydrophobic groups, for example two aliphatic hydrocarbon radicals, which can be substituted by one or two optionally substituted, monocyclic, aliphatic or aromatic hydrocarbon radicals or by an optionally substituted, monocyclic, aromatic, partially saturated or saturated heterocycle, or R_a and R_b together represent an optionally substituted, monocyclic, aromatic, saturated, partially saturated or benzo-fused heterocycle. The hydrophilic group is a group of the formula



in which R_c and R_d, independently of one another, each represents hydrogen or C_1-C_4-alkyl, preferably methyl.

In a substituted ammonium compound of the formula 1 that can be used as a medicament, in case c) R_a, R_b and R_c form the hydrophobic group and together represent an optionally substituted, aromatic, partially saturated or benzo-fused heterocycle. The

hydrophilic group is a group of the formula

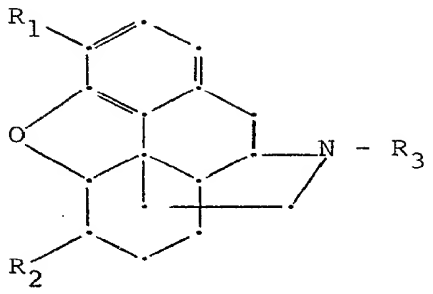
$$\geq \overset{\oplus}{N} - R_d$$

in which R_d represents hydrogen or C_1-C_4-alkyl, preferably methyl.

$X^{\ominus}$ is the anion of a pharmaceutically acceptable acid, for example a mineral acid, for example the chloride, hydrogen sulphate or dihydrogen phosphate ion, the bromide or iodide ion, or the anion of an organic acid, for example a lower alkanecarboxylic acid, for example the acetate ion, of an unsaturated carboxylic acid, for example the fumarate or maleate ion, of a hydroxy acid, for example the lactate, tartrate or citrate ion, or of an aromatic acid, for example the salicylate ion.

An amphiphatic, substituted ammonium compound of the formula 1 that can be used as a medicament, or the corresponding amino compound that can be converted into the ammonium compound by salt formation, is, for example, a compound selected from the group comprising parasympathomimetics having quaternary or tertiary ammonium groups, for example acetylcholine chloride, methacholine chloride, carbachol, muscarine, pilocarpine or arecoline; choline esterase inhibitors having two tertiary amino groups, for example phyostigmine, or having a quaternary ammonium group, for example neostigmine bromide or pyridostigmine bromide; neurotransmitters having a primary amino group, for example serotonin or histamine; serotonin-antagonists in which the hydrophobic group has an indol-3-ylethyl structure and the hydrophilic group is a primary or tertiary amino group, for example tryptamine, bufotenine or psilocybin; analgesics of the morphine type having a tertiary amino group and their

antagonists, for example of the formula



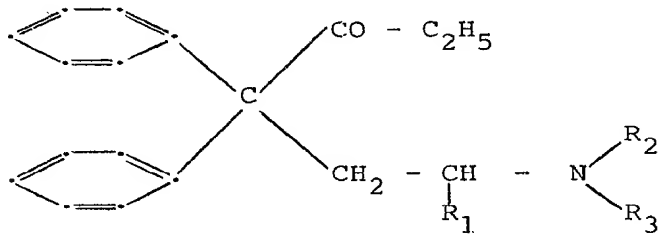
(1.1)

in which R_1, R_2 and R_3 have the meanings given in the following list:

R_1	R_2	R_3	Name
-OH	-OH	$-CH_3$	Morphine
-OH	=O	$-CH_3$	Hydromorphone
-OH	=O	$-CH_3$	Oxymorphone
-OH	-H	$-CH_3$	Levorphanol
$-OCH_3$	-OH	$-CH_3$	Codeine
$-OCH_3$	=O	$-CH_3$	Hydrocodone
$-OCH_3$	=O	$-CH_3$	Oxycodone
-OH	-OH	allyl	Nalorphine
-OH	=O	allyl	Naloxone
-OH	=O	cyclopropylmethyl	Naltrexone
-OH	$-OCH_3$	cyclopropylmethyl	Buprenophine
-OH	-H	cyclobutylmethyl	Butorphanol
-OH	-OH	cyclobutylmethyl	Nalbuphine
-2-(morpholin-1-yl)-ethyl	-OH	$-CH_3$	Pholcodine

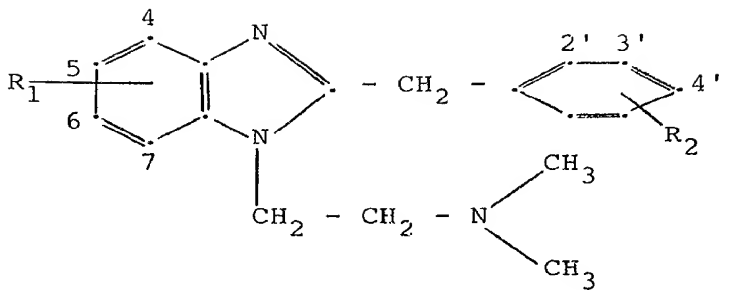
analgesics of the benzomorphan type having a tertiary amino group, for example metazocine, pentazocine or cyclazocine; analgesics of the pethidine type, for

example pethidine, cetobemidon, alphaphrodine, ethoheptazine, prodilidine or profadol; analgesics of the methadone type in which the hydrophobic group is, for example, a 1,1-diphenyl-1-lower alkyl-2-butanone radical and the hydrophilic group is dimethylamino, morpholino or piperidino, for example hydrochlorides of compounds of the formula



(1.2)

in which R_1 represents hydrogen or methyl, R_2 and R_3 each represents methyl, or R_2 and R_3 together represent morpholino or piperidino, for example methadone, normethadone, isomethadone, dipipanone, phenadoxone or analogues thereof having a pseudo-methadone structure, for example dimephethanol or dextromoramide; analgesics similar to morphine having an aliphatic or cycloaliphatic tertiary amino group, for example D-propoxyphene, 1-benzyl-2-dimethylamino-methyl-1-propanoyloxytetralin, tramadol, dimethylthiambutene, diampromide, phenampromide, propiram, tilidine, metopholine or etonitazene; analgesics of the benzimidazole type, for example of the formula

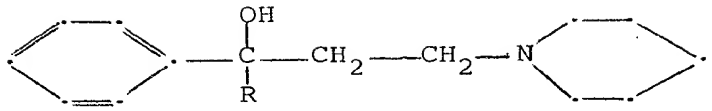


(1.3)

in which R_1 represents 5-, 6- or 7-nitro, R_2 represents hydrogen, 3'- or 4'-methoxy, 4'-ethoxy, 4'-isopropoxy, 4'-methyl or 4'-chloro; local anaesthetics in which R_a and R_b in the formula 1 together with the nitrogen form a piperidyl radical that is substituted by a lower alkylene bridge, for example 1,3-propylene, that is itself substituted by a methoxycarbonyl and a benzoyloxy group, for example pseudococaine or cocaine; local anaesthetics in which the hydrophobic group R_a in the formula (1) is, for example, a 4-aminobenzoyloxyethyl, 4-amino-2-chloro-, 2-n-butoxy- or 2-hydroxy-benzoyloxyethyl, 4-amino-3-n-butoxybenzoyloxyethyl, 3-amino-4-n-butoxy-benzoyloxyethyl, 2-aminobenzoyloxyethyl, 2-(4-amino-benzoyloxy)-6-methyl-n-pentyl, 4-aminobenzoyloxy-n-propyl, 4-n-butylaminobenzoyloxyethyl, 4-n-butyl-2-hydroxybenzoyloxyethyl, 3-(4-n-propoxybenzoyloxy-2-hydroxy)-propyl, 2-n-benzoyloxy-n-propyl, 2-(2-acetoxybenzoyloxy)-n-propyl, benzoyloxy-n-propyl, 4-cyclohexyloxybenzoyloxyethyl, 4-ethyl- or 4-n-butyl-benzoyloxyethyl, 2-n-butoxyquinol-4-ylcarbonyloxyethyl, 2,4-dimethylanilinocarbonylmethyl, 2-ethyl-, 2-chloro- or 2-methoxycarbonylethyl-4-methylanilinocarbonyl-methyl, 1-(2-methylanilinocarbonyl)-ethyl, (2-ethoxy-carbonyl-4-methylthien-3-ylaminocarbonyl)-ethyl,

2,3-dianilinocarbonyloxypropyl, 4-n-propyl- or 4-n-butyl-benzoylethyl, 4-phenoxymethylphenyl-n-butyl, 4-n-butoxyphenoxy-n-propyl, 2-n-butylquinol-8-yloxymethyl or 8-benzoyloxycarbonyl-1,2,3,4-tetrahydronaphth-2-yl group, and the hydrophilic group is lower alkylamino, for example methyl-, ethyl-, isopropyl- or n-butyl-amino, di-lower alkylamino, for example dimethyl-, diethyl- or di-n-propyl-amino, cyclohexylamino, 1-methylpiperid-2-yl, piperid-1- or -2-yl or morpholin-1-yl, for example local anaesthetics, neuroleptics and/or thymoleptics that have become known under the names procaine, chloroprocaine, hydroxyprocaine, propoxycaine, oxybuprocaine, propoxymetacaine, piridocaine, leucinocaine, butacaine, tetracaine, hydroxytetracaine, cornecaine, edan, piperocaine, cyclomethycaine, parethoxycaine, stadacain, cinchocaine, lidocaine, pyrrocaine, granocaine, butanilicaine, tolycaine, mepivacaine, bupivacaine, prilocaine, carticaine, dipiperidon, propicocaine, dyclonine, pramocaine, fomocaine or quinisocaine, in which the non-polar, hydrophobic group R_a of the formula 1 is a lower alkyl radical, for example ethyl, n-propyl, isopropyl or n-butyl, or hydroxy-lower alkyl, for example 2-hydroxy-n-propyl, that is substituted by 2-cyano-, 2-methoxy-, 2-chloro-, 2-trifluoromethyl-, 2-methylthio-, 2-acetyl- or 2-ethyl-10H-phenothiazin-10-yl, 9H-acridin-10-yl, 5H-dibenzo[b,f]azepin-5-yl, 7-chloro-10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl, 5,10-dihydro-5-methyl-11-dibenzo[b,e]-1,4-diazepin-11-onyl, 2-chloro-, 2-trifluoromethyl- or 2-dimethylaminosulphonyl-9H-thioxanthen-9-ylidene, 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl or by 10H-pyrido[3,2--b]-[1,4]benzothiazin-10-yl, and the polar hydrophilic group represents amino, lower alkylamino, for example

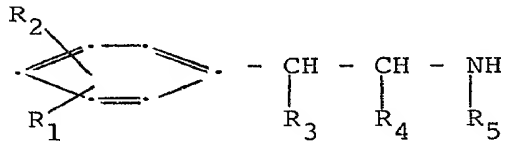
methylamino, di-lower alkylamino, for example dimethyl- or diethyl-amino, tri-lower alkylamino, for example trimethyl- or triethyl-amino, piperidino or 4-hydroxy-ethylpiperazino, for example profenamine, promethazine, periciazine, perimethazine, chlorpromazine, perphenazine, prochlorperazine, triflumproazine, trifluoroperazine, fluphenazine, thioridazine, mesoridazine, piperacetazine, acetophenazine, ethymemazine, dimethacrine, opipramol, clomipramine, imipramine, desimipramine, trimipramine, chloroprothixene, thiothixene, amitriptyline, nortriptyline, doxepin, thiepin, protriptyline or prothipendyl; antidepressants having a tertiary amino group selected from the group comprising citalopram, zimelidine, trebenzomin, viloxazine, nomifensine and femoxetin; thymeretics having a primary or methyl- and propargyl-substituted amino group, for example tranylcypromine, pargyline or etryptamine; sedatives in which the hydrophobic group R_a in the formula 1 is the 2-(7-chloro-5-o-fluorophenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-on-1-yl)-ethyl radical and the hydrophilic group is diethylamino, for example flurazepam; psychodysleptics having a β-phenylethyl-amine structure, for example mescaline; psychodysleptics in which the hydrophobic group R_a in the formula 1 is an ethyl radical substituted by a 3-indole radical, for example N_α,N_α-dimethyltrypt-amine, bufotenine, psilocin or psilocylein; psychodysleptics in which R_a and R_b in the formula 1 together with the nitrogen atom form a morpholine or pyrrolidine ring that is substituted by 1,3-lower alkylene, for example scopolamine or atropine; anticholinergics having an atropine structure, for example benzatropine; anticholinergics (agents against Parkinson's Disease) of the formula



(1.4)

in which R represents cyclohexyl, cyclopentyl, phenyl or norborn-5-en-2-yl, for example trihexyphenidyl, cycrimine, pridinol or biperidin, and analogues, such as procyclidine; anticholinergics having a tertiary amino group, for example caramiphen, phenglutarimide, orphenadrine or chlorphenoxamine; central analeptics having a morpholine group, for example doxapram; psychoanaleptics having a phenylaminopropane structure, for example amphetamine, methamphetamine, propylhexedrine, prolintane, fencamfamine, methylphenidate, pipradrol or phenmetrazine; psychoanaleptics having a 4-chlorophenoxyacetoxyethyl group as hydrophobic group and a dimethylamino group as hydrophilic group, for example meclofenoxate; vasodilatators having a tertiary amino group, for example naftidrofuryl; appetite suppressants having an amphetamine structure, for example dexamphetamine, phentermine, chlorophentermine, fenfluramine, amfepramone, phenmetrazine or phendimetrazine; muscle relaxants having a hydrophobic group and several quaternary amino groups, for example tubocumarin, alcuronium chloride, gallamine triethiodide, hexacarbacholine bromide, pancuronium bromide, suxamethonium chloride or decamethonium bromide; neurotropic spasmolytics having quaternary amino groups, for example scopolamine butyl bromide, bevonium methyl sulphate, valethamate bromide or

methanteline bromide; musculotropic spasmolytics having tertiary amino groups, for example camylofine, hexahydroadiphenine, adiphenine or fencarbamide; 4-aminoquinoline antirheumatics, for example chloroquine; anti-oestrogens having a tertiary amino group, for example tamoxifen or ethamoxytriphetol; histamine H_1-receptor antagonists (antihistamines) having an ethylenediamine group, for example phenbenzamine, tripelenamine, chloropyramine, mepyramine, metaphenilen, metapyrilene, chloropyrilene, histapyrrodine, bamipine, thenalidine, clemizole, methdilazine, isothipendyl or oxomenazine, a 2-aminoethanol group, for example diphenhydramine, medrylamine, chlorophenoxamine, silachlorophenoxamine, carbinoxamine, diphenpyraline, clemastine or amethobenzepin, or a 3-aminopropane group, for example pheniramine, chlorophenamine, bromopheniramine, triprolidine, cycliramine, phenindamine, dimetindene, cyproheptadine or ketotifen; sympathomimetics of the formula

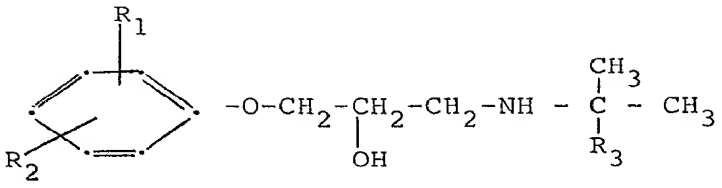


(1.5)

in which R_1, R_2, R_3, R_4 and R_5 have the following meanings:

R_1	R_2	R_3	R_4	R_5	Name
3-OH	4-OH	-OH	-H	$-CH_3$	Epinephrine (Adrenaline)
3-OH	4-OH	-OH	-H	-H	Norepinephrine (Noradrenaline)
3-OH	4-OH	-H	-H	-H	Dopamine
3-OH	4-OH	-OH	$-CH_3$	-H	Nordefrin
3-OH	4-OH	-OH	$-C_2H_5$	-H	Ethylnorepine-phrine
3-OH	4-OH	-OH	-H	$-CH(CH_3)_2$	Isoprenaline
3-OH	4-OH	-OH	$-C_2H_5$	$-CH(CH_3)_2$	Isoethorine
3-OH	4-OH	-OH	-H	$-CH(CH_3)_2$	Metaproterenol
3-OH	5-OH	-OH	-H	$-C(CH_3)_3$	Orciprenaline
3-OH	-H	-OH	$-CH_3$	-H	Metaraminol
3-OH	-H	-OH	-H	$-CH_3$	Phenylephrine
4-OH	-H	-H	-H	-H	Hydroxy-amphetamine
$2-OCH_3$	-H	-H	$-CH_3$	$-CH_3$	Methoxy-phenamine
$2-OCH_3$	$5-OCH_3$	-OH	$-CH_3$	-H	Methoxamine
$3-CH_2OH$	4-OH	-OH	-H	$-C(CH_3)_3$	Albuterol
-H	-H	-OH	$-CH_3$	$-CH_3$	Ephedrine
-H	-H	-OH	$-CH_3$	-H	Norephedrine
$3-CF_3$	-H	-H	$-CH_3$	$-C_2H_5$	Fenfluramine
-H	-H	-OH	$-CH_3$	-H	Phenylpropanol-amine
4-OH	-H	-OH	$-CH_3$	$-CH_3$	Pholedrine
4-OH	-H	-OH	$-CH_3$	-H	Tyramine
3-Cl	4-Cl	-OH	-H	$-C(CH_3)_3$	Dichloro-isoprenaline
4-OH	-H	-OH	-H	$-CH_3$	Norfenefrine
4-OH	-H	-OH	-H	-H	Octopamine
3-OH	-H	-OH	-H	$-C_2H_5$	Etilefrin,

ß-receptor blockers of the formula:



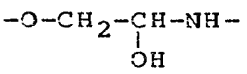
(1.6)

in which R_1, R_2 and R_3 have the following meanings:

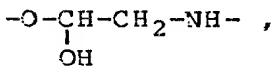
R_1	R_2	R_3	Name
2-acetyl	4-n-butyryl-amino	H	Acebutolol
4-carbamoylmethyl	H	H	Atenolol
4-(2-carbamoylethyl)	H	H	Metoprolol
3-methyl	H	H	Toliprolol
2-allyl	H	H	Alprenolol
2-allyloxy	H	H	Oxprenolol
2-cyano	H	methyl	Bunitrolol
2-chloro	5-methyl	methyl	Bupranolol
3-(N-cyclohexyl-N'-ureido)	H	methyl	Talinolol
2-cyclopentyl	H	methyl	Phenbutolol
2-tetrahydrofur-2-ylmethoxy	H	methyl	Bufetolol
2-pyrrol-1-yl	H	H	
4-(2-methylthio-ethoxy)	H	H	
4-OH	H	H	Varbian, R,S-form, S-form,

ß-blockers having a bicyclic, condensed aryloxy radical, for example the naphthyloxy, indolyloxy, 2-

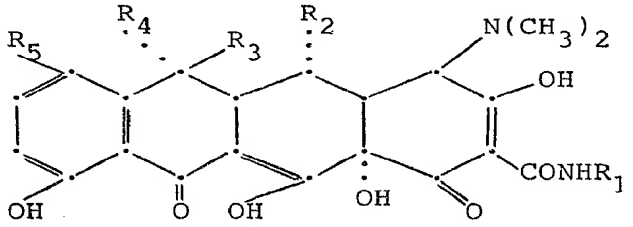
methylindolyloxy, 1,2,3,4-tetrahydronaphth-2,3-diol-1-yl or 1,2,3,4-tetrahydronaphth-5-on-1-yl radical, for example propanolol, indenolol, pindolol, mepindolol, nadolol or bunolol, and ß-blockers in which the segment



has been replaced by



for example sotalol, nifenalol, labetalol or bufuralol, compounds having an action on peripheral noradrenaline storers, for example compounds of the reserpine type, for example reserpine, rescinnamine or syringopine; tetracycline antibiotics of the formula



(1.7)

in which R_1 represents hydrogen or pyrrolidin-1-ylmethyl, R_2 represents hydrogen or hydroxy, R_3 represents hydrogen, hydroxy or methyl, R_4 represents hydrogen or methyl, and R_5 represents hydrogen, chlorine or dimethylamino, for example chlorotetracycline, oxytetracycline, tetracycline, demethylchlortetracycline, metacycline, doxycycline, minocycline or

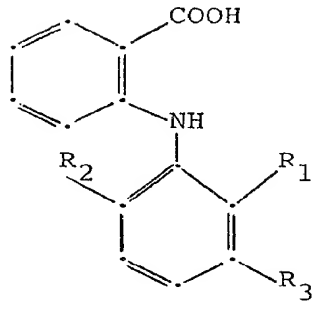
rolitetracycline; antimalarial agents of the quinine type, for example conquinidine, quinidine or cinchonine, and analogues having an 8-aminoquinoline structure, for example pamaquine, primaquine or pentaquine, a 4-aminoquinoline or 9-aminoacridine structure, for example chloroquine, santoquin, hydroxychloroquine, amodiaquin or mepacrine, a 1,3,5-triazine or pyrimidine structure, for example proguanil or progianil; anti-schistosomatics in which the hydrophobic, non-polar group is optionally 6-chloro- and/or 4-methyl- or 4-hydroxymethyl-substituted xanthonyl or thioxanthonyl, and the hydrophilic, polar group is diethylamino, for example lucanthone, hycanthone, myracil A or B; antiviral agents of the cyclic amines type, for example amantadine, cyclooctylamine or rimantadine, and glucocorticoids that are esterified in the 21-position by an amino acid, for example prednisolone diethylaminoacetate.

In a carboxylic acid salt of the formula 2 that can be used as a medicament, the hydrophobic group R_a is an aliphatic hydrocarbon radical that can be substituted by an optionally substituted, monocyclic, aromatic hydrocarbon radical or by an optionally substituted, bi- or tri-cyclic, aromatic or partially saturated hydrocarbon radical, by an optionally substituted, monocyclic, aromatic or partially saturated heterocycle or by an optionally substituted, bi- or tri-cyclic, aromatic, partially saturated or benzo-fused heterocycle or by a steroid radical, or R_a is an optionally substituted, monocyclic, aromatic hydrocarbon radical, an optionally substituted, bi- or tri-cyclic, aromatic or partially saturated hydrocarbon radical, an optionally substituted, monocyclic, aromatic or partially saturated heterocycle or an optionally substituted, bi- or tri-cyclic, aromatic,

partially saturated or benzo-fused heterocycle.

The cation $Y^{\oplus}$ of a pharmaceutically acceptable base is, for example, an alkali metal ion, for example a lithium, sodium or potassium ion, an alkaline earth metal ion, for example a magnesium or calcium ion, or an ammonium or mono-, di- or tri-C_1-C_4-alkylammonium ion, for example a trimethyl-, ethyl-, diethyl- or triethyl-ammonium ion, a 2-hydroxyethyl-tri-C_1-C_4-alkylammonium ion, for example cholinyl, or the cation of a basic amino acid, for example lysine or arginine.

Carboxylic acid salts of the formula 2 having biological activity or carboxylic acids that can be converted into them by salt formation are, for example, salts of glucocorticoids that are esterified in the 21-position by a dicarboxylic acid, for example methylprednisolone sodium succinate, prednisolone sodium succinate, short-term narcotics of the 3,20-dioxo-5β-pregnane type that can be esterified by succinic acid, for example hydroxydione succinate sodium or 11,20-dioxo-3α-hydroxy-5α-pregnane, for example alphaxolone, or the 21-compound, for example alphadolone; salts of choleritics, for example cholic acid salts or deoxycholic acid salts; analgesics, for example salts of substituted phenylacetic acids or 2-phenylpropionic acids, for example alclofenac, ibufenac, ibuprofen, clindanac, fenclorac, ketoprofen, fenoprofen, indoprofen, fenclofenac, diclofenac, flurbiprofen, pirprofen, naproxen, benoxaprofen, carprofen or cicloprofen; analgesically active anthranilic acid derivatives, for example of the formula



(2.1)

in which R_1, R_2 and R_3, independently of one another, each represents hydrogen, methyl, chlorine or trifluoromethyl, for example mefenamic acid, flufenamic acid, tolfenamic acid or meclofenamic acid; analgesically active anilino-substituted nicotinic acid derivatives, for example miflumic acid, clonixin or flunixin; analgesically active heteroarylacetic acids or 2-heteroarylpropionic acids having a 2-indol-3-yl or pyrrol-2-yl radical, for example indomethacin, oxmetacin, intrazol, acemetazin, cinmetacin, zomepirac, tolmetin, colpirac or tiaprofenic acid; analgesically active indenylacetic acids, for example sulindac; analgesically active heteroaryloxyacetic acids, for example benzadac, prostanoic acids that stimulate the smooth musculature, for example PGE_2 (dinoprostone), $PGF_{2\alpha}$ (dinoprost), 15 (S)-15-methyl-PGE_2, 15 (S)-15-methyl-$PGF_{2\alpha}$ (carboprost), ($\pm$)15 (Xi)-15-methyl-13,14-dihydro-11-deoxy-PGE_1 (deprostil), 15 (S)-15-methyl-11-deoxy-PGE_1 (doxaprost), 16,16-dimethyl-PGE_2, 17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$, 16-phenoxy-17,18,19,20-tetranor-$PGF_{2\alpha}$, for example cloprostenol or fluprostenol, or N-methylsulphonyl-16-phenoxy-17,18,-19,20-tetranor-$PGF_{2\alpha}$(sulproston); bacteriostatics, for example salts of nalidixic acid derivatives, for

example nalidixic acid, cinoxacin, oxolinic acid, pironidic acid or pipenidic acid, penicillanic acid and cephalosporanic acid derivatives having antibiotic activity with 6β- or 7β-acylamino groups, which are present in fermentatively, semi-synthetically or totally synthetically obtainable 6β-acylamino-penicillanic acid or 7β-acylaminocephalosporanic acid derivatives or 7β-acylaminocephalosporanic acid derivatives modified in the 3-position, for example penicillanic acid derivatives that have become known under the names penicillin G or V, phenethicillin, propicillin, nafcillin, oxacillin, cloxacillin, dicloxacillin, flucloxacillin, cyclacillin, epicillin, mecillinam, methicillin, azlocillin, sulbenicillin, ticarcillin, mezlocillin, piperacillin, carindacillin, azidocillin or ciclazillin, or cephalosporin derivatives that have become known under the names cefaclor, cefuroxime, cefazlur, cephacetrile, cefazolin, cephalexin, cefadroxil, cephaloglycin, cefoxitin, cephaloridine, cephsulodin, cefotiam, ceftazidine, cefonicid, cefotaxime, cefmenoxime, ceftizoxime, cephalothin, cephradine, cefamandol, cephanone, cephapirin, cefroxadin, cefatrizine, cefazedone, ceftrixon or ceforanid, and other β-lactam antibiotics, for example moxalactam, clavulanic acid, nocardicine A, sulbactam, aztreonam or thienamycin, or antineoplastics having a 4-[bis-(2-chloroethyl)-amino-phenyl]-butyric acid structure, for example chlorambucil, or antineoplastics having two carboxy groups, for example methotrexate.

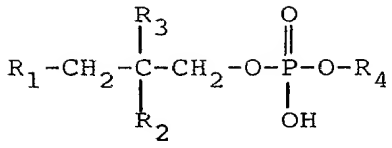
Compounds of the formula 3 having a biological activity are, for example, neurotransmitters in which the hydrophobic group is methyl substituted by hydroxyphenyl, for example L-tyrosine, L-dopa, α-methyldopa or metirosine, thyroid hormones having

iodine-substituted phenyl radicals, for example levothyrosine, diiodotyrosine or liothyronine, or antineoplastics having an amino acid structure, for example melphalen.

In a compound of the formula 4 having biological activity the non-polar, hydrophobic group R_a is a glucocorticoid radical and $X^{\oplus}$ is sodium, for example betamethasone disodium phosphate, dexamethasone disodium phosphate, cortisone phosphate, hydrocortisone phosphate, prednisolone disodium phosphate or paramethasone-21-disodium phosphate.

Salt-type compounds having a hydrophobic group and an imidazoline, imidazolidine or hydrazino group as hydrophilic group are, for example, salts of antidepressantly active hydrazine derivatives, for example iproniazid, nialamide, isocarboxazid, phenelzine, pheniprazine, mebanazine or fenoxypropazine; α-sympathomimetics having an imidazoline structure, for example naphazoline, tetryzolin, tramazoline, xylometazoline or oxymetazoline; α-sympatholytics having an imidazoline structure, for example phentolamine or tolazoline, or centrally active antihypertensives having an imidazoline structure, for example clonidine, tolonidine or flutonidine, or vasodilatators having a hydrazino group, for example dihydralazine, hydralazine or picodralazine.

A phospholipid (II) that is mixed homogeneously with the amphiphatic compound (I) having biological activity has, for example, the formula



(5)

in which one of the radicals R_1 and R_2 represents hydrogen, hydroxy or C_1-C_4-alkyl, and the other radical represents alkyl, alkenyl, alkoxy, alkenyloxy or acyloxy each having from 10 to 20 carbon atoms, or both radicals R_1 and R_2 represent alkyl, alkenyl, alkoxy, alkenyloxy or acyloxy each having from 10 to 20 carbon atoms, R_3 represents hydrogen or C_1-C_4-alkyl, and R_4 represents hydrogen, optionally substituted C_1-C_7-alkyl or a carbohydrate radical having from 5 to 12 carbon atoms or, if both radicals R_1 and R_2 represent hydrogen or hydroxy, R_4 represents a steroid radical, or is a salt thereof.

In a phospholipid of the formula 5, R_1, R_2 or R_3 having the meaning C_1-C_4-alkyl is preferably methyl, but may also be ethyl, n-propyl, or n-butyl.

Alkyl R_1 or R_2 is preferably straight-chained with an even number of from 10 to 20 carbon atoms, for example n-decyl, n-dodecyl (lauryl), n-tetradecyl (myristyl), n-hexadecyl (cetyl), n-octadecyl (stearyl) or n-eicosyl (arachinyl).

Alkenyl R_1 and/or R_2 is preferably straight-chained with an even number of from 12 to 20 carbon atoms and a double bond, for example 9-cis-dodecenyl (lauroleyl), 9-cis-tetradecenyl (myristoleyl), 9-cis-hexadecenyl (palmitoleinyl),

6-cis-octadecenyl (petroselinyl), 6-trans-octadecenyl (petroselaidinyl), 9-cis-octadecenyl (oleyl), 9-trans-octadecenyl (elaidinyl) or 9-cis-eicosenyl (gadoleinyl).

Alkoxy R_1 and/or R_2 is preferably straight-chained with an even number of from 10 to 20 carbon atoms, for example n-decyloxy, n-dodecyloxy (lauryloxy), n-tetradecyloxy (myristyloxy), n-hexadecyloxy (cetyloxy), n-octadecyloxy (stearyloxy) and n-eicosyloxy (arachinyloxy).

Alkenyloxy R_1 and/or R_2 is preferably straight-chained with an even number of from 12 to 20 carbon atoms, for example 9-cis-dodecenyloxy (lauroleyloxy), 9-cis-tetradecenyloxy (myristoleyloxy), 9-cis-hexadecenyloxy (palmitoleinyloxy), 6-cis-octadecenyloxy, (petroselinyloxy), 6-trans-octadecenyloxy (petroselaidinyloxy), 9-cis-octadecenyloxy (oleyloxy), 9-trans-octadecenyloxy (elaidinyloxy) and 9-cis-eicosenyl (gadoleinyloxy).

Acyloxy R_1 and/or R_2 is preferably straight-chained with an even number of from 10 to 20 carbon atoms, for example alkanoyloxy or alkenoyloxy, preferably n-decanoyloxy, n-dodecanoyloxy (lauroyloxy), n-tetradecanoyloxy (myristoyloxy), n-hexadecanoyloxy (palmitoyloxy), n-octadecanoyloxy (stearoyloxy) and n-eicosoyloxy (arachinoyloxy).

Alkenoyloxy R_1 and/or R_2 is preferably straight-chained with an even number of from 10 to 20 carbon atoms, for example 9-cis-dodecenyloxy (lauroleoyloxy), 9-cis-tetradecenoyloxy (myristoleoyloxy), 9-cis-hexadecenoyloxy (palmitoleinoyloxy), 6-cis-octadecenoyloxy (petroselinoyloxy), 6-trans-octadecenoyloxy (petroselaidinoyloxy), 9-cis-octadecenoyloxy (oleoyloxy), 9-trans-octadecenoyloxy

(elaidinoyloxy) and 9-cis-eicosenoyloxy (gadoleinoyloxy).

Optionally substituted C_1-C_7-alkyl R_4 is, for example, methyl, ethyl, isopropyl, n-propyl, isobutyl or n-butyl which can be substituted by acidic groups, for example carboxy or sulpho, by acidic and basic groups, for example carboxy and amino, the amino group being in the α-position to the carboxy group, by free or etherified hydroxy groups, it being possible for two etherified hydroxy groups to be bonded to one another by a bivalent hydrocarbon radical, for example methylene, ethylene, ethylidene, 1,2-propylene or 2,2-propylene, or by halogen, for example chlorine or bromine, by lower alkoxycarbonyl, for example methoxy- or ethoxy-carbonyl, or by lower alkanesulphonyl, for example methanesulphonyl.

Substituted C_1-C_7-alkyl R_4 is, for example, carboxy-lower alkyl, for example carboxymethyl, 2-carboxyethyl or 3-carboxy-n-propyl, ω-amino-ω-carboxy-lower alkyl, for example 2-amino-2-carboxyethyl or 3-amino-3-carboxy-n-propyl, hydroxy-lower alkyl, for example 2-hydroxyethyl or 2,3-dihydroxypropyl, lower alkoxy-lower alkyl, for example methoxy- or ethoxy-methyl, 2-methoxyethyl or 3-methoxy-n-propyl, lower alkylenedioxy-lower alkyl, for example 2,3-ethylenedioxypropyl or 2,3-(2,2-propylene)-dioxy-propyl, or halo-lower alkyl, for example chloro- or bromo-methyl, 2-chloro- or 2-bromo-ethyl, 2- or 3-chloro- or 2- or 3-bromo-n-propyl.

Substituted C_1-C_7-alkyl R_4 is preferably ethyl substituted by tri-lower alkylammonium, for example trimethyl- or triethyl-ammonium, for example 2-trimethylammonium-ethyl or 2-ammonium-ethyl, or 15, for example ω-amino-ω-carboxy-lower alkyl, for example 2-amino-2-carboxyethyl.

A carbohydrate radical R_4 having from 5 to 12 carbon atoms is, for example, a natural monosaccharide radical that is derived from a pentose or hexose present in the form of aldose or ketose.

A pentose present in the form of aldose is, for example, D-ribose, D-arabinose, D-xylose or D-lyxose.

A pentose present in the form of ketose is, for example, D-ribulose or D-xylulose.

A hexose present in the form of aldose is, for example, D-allose, D-altrose, D-glucose, D-mannose, D-galactose or D-talose.

A hexose present in the form of ketose is, for example, D-psicose, D-fructose, D-sorbose or D-tagatose.

A hexose is preferably present in cyclic form, for example in the form of pyranose (aldose), for example α- or β-D-fructose. The pyranosyl radical is preferably esterified by the phosphatidyl group by way of the hydroxy group located in the 1- or 6-position and the furanosyl radical is preferably esterified by way of the hydroxy group in the 1- or 5-position.

A carbohydrate radical R_4 having from 5 to 12 carbon atoms is also a natural disaccharide radical, for example a disaccharide radical that is formed from two hexoses and which is formed, for example, by condensation of two aldoses, for example D-glucose or D-galactose, or an aldose, for example D-glucose, with a ketose, for example fructose. Disaccharides formed from two aldoses, for example lactose or maltose, are preferably esterified by the phosphatidyl group by way of the hydroxy group located in the 6-position of the pyranosyl radical in question. Disaccharides formed from an aldose and a ketose, for example saccharose, are preferably esterified by the phosphatidyl group by way of the hydroxy group located in the 6-position of

the pyranosyl radical or the hydroxy group located in the 1-position of the furanosyl radical.

A carbohydrate radical R_4 having from 5 to 12 carbon atoms is also a derivatised mono- or di-saccharide radical in which, for example, the aldehyde group and/or one or two terminal hydroxy groups are oxidised to carboxy groups, for example D-gluconic, D-glucaric or D-glucoronic acid radicals which are preferably present in the form of cyclic lactone radicals. It is likewise possible in a derivatised mono- or di-saccharide radical for aldehyde or keto groups to be reduced to hydroxy groups, for example inositol, sorbitol or D-mannitol, or for hydroxy groups to be replaced by hydrogen, for example desoxy-sugars, for example 2-desoxy-D-ribose, L-rhamnose or L-fucose, or by amino groups, for example an amino-sugars, for example D-glucosamine or D-galactosamine.

A carbohydrate radical R_4 can also be a cleavage product formed by the reaction of one of the mentioned mono- or di-saccharides with a strong oxidising agent, for example periodic acid.

A steroid radical R_4 is, for example, a sterol radical that is esterified by the phosphatidyl group by way of the hydroxy group located in the 3-position of the steroid nucleus.

A sterol radical is, for example, the lanosterol, sitosterol, coprostanol, cholestanol, glycocholic acid, ergosterol or stigmasterol radical, preferably the cholesterol radical.

If R_4 represents a steroid radical, R_1 and R_2 are preferably hydroxy and R_3 is hydrogen.

Phospholipids of the formula 5 can be in the form of free acids or in the form of salts. Salts are formed by reaction of the free acid of the formula II with a base, for example a dilute, aqueous solution of

an alkali metal hydroxide, for example lithium, sodium or potassium hydroxide, magnesium or calcium hydroxide, a dilute aqueous ammonia solution or an aqueous solution of an amine, for example a mono-, di- or tri-lower alkylamine, for example ethyl-, diethyl- or triethyl-amine, 2-hydroxyethyl-tri-C_1-C_4-alkyl-amine, for example choline, and a basic amino acid, for example lysine or arginine.

A phospholipid of the formula 5 has especially two acyloxy radicals R_1 and R_2, for example alkanoyloxy or alkenoyloxy, for example lauroyloxy, myristoyloxy, palmitoyloxy, stearoyloxy, arachinoyloxy, oleoyloxy, linoyloxy or linoleoyloxy, and is, for example, natural lecithin (R_3 = hydrogen, R_4 = 2-trimethylammonium ethyl) or cephalin (R_3 = hydrogen, R_4 = 2-ammonium ethyl) having different acyloxy radicals R_1 and R_2, for example egg lecithin or egg cephalin or lecithin or cephalin from soya beans, synthetic lecithin or cephalin having different or identical acyloxy radicals R_1 and R_2, for example 1-palmitoyl-2-oleoyl lecithin or cephalin or dipalmitoyl, distearoyl, diarachinoyl, dioleoyl, dilinoyl or dilinoleoyl lecithin or cephalin, natural phosphatidyl serine (R_3 = hydrogen, R_4 = 2-amino-2-carboxyethyl) having different acyloxy radicals R_1 and R_2, for example phosphatidyl serine from bovine brain, synthetic phosphatidyl serine having different or identical acyloxy radicals R_1 and R_2, for example dioleoyl-, dimyristoyl- or dipalmitoyl-phosphatidyl serine, or natural phosphatidic acid (R_3 and R_4 = hydrogen) having different acyloxy radicals R_1 and R_2.

A phospholipid of the formula 5 is also a phospholipid in which R_1 and R_2 represent two identical alkoxy radicals, for example n-tetradecyloxy or n-hexadecyloxy (synthetic ditetradecyl or dihexa-

decyl lecithin or cephalin), R_1 represents alkenyl and R_2 represents acyloxy, for example myristoyloxy or palmitoyloxy (plasmalogen, R_3 = hydrogen, R_4 = 2-trimethylammonium ethyl), R_1 represents acyloxy and R_2 represents hydroxy, (natural or synthetic lysolecithin or lysocephalin, for example 1-myristoyl- or 1-palmitoyl-lyso-lecithin or -cephalin, natural or synthetic lysophosphatidyl serine, R_3 = hydrogen, R_4 = 2-amino-2-carboxyethyl, for example lysophosphatidyl serine from bovine brain or 1-myristoyl- or 1-palmitoyl-lysophosphatidyl serine, synthetic lysophosphatidyl glycerine, R_3 = hydrogen, R_4 = $CH_2OH-CHOH-CH_2-$, natural or synthetic lysophosphatidic acid, R_3 = hydrogen, R_4 = hydrogen, for example egg lysophosphatidic acid or 1-lauroyl-, 1-myristoyl- or 1-palmitoyl-lysophosphatidic acid).

A lipid that is analogous to a phospholipid and can be homogeneously mixed with the amphiphatic compound (I) having biological activity instead of the phospholipid (II) is, for example, a lysolecithin analogue, for example 1-lauroyl-1,3-propanediol-3-phosphoryl choline, a monoglyceride, for example monoolein or monomyristin, a cerebroside, a ganglioside or a glyceride that does not contain a free or esterified phosphoryl or phosphonyl group in the 3-position, for example a diacylglyceride or 1-alkenyl-1-hydroxy-2-acylglyceride having the mentioned acyl or alkenyl groups in which the 3-hydroxy group is etherified by one of the mentioned carbohydrate radicals, for example a galactosyl radical, for example monogalactosyl glycerine.

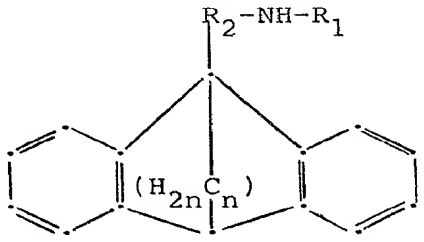
Together with the amphiphatic compound (I) having biological activity, the phospholipid (II) or the analogous lipid, it is also possible to add to the homogeneous mixture neutral lipids that are contained

in cell membranes and are soluble only in non-polar, organic solvents, for example in chloroform.

Such neutral lipids are, for example, steroids, for example oestradiol, or sterols, for example cholesterol, β-sitosterol, desmosterol, 7-keto-cholesterol or 8-cholestanol, fat-soluble vitamins, for example vitamins A_1 and A_2 or vitamin E, K_1, K_2, D_2 or D_3.

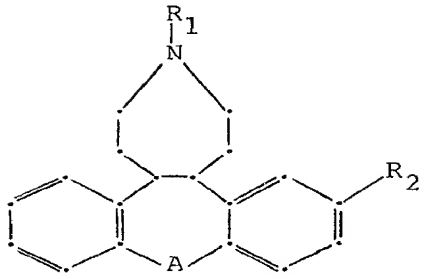
The lipids mentioned hereinbefore and hereinafter having a chiral carbon atom can be present both in the form of racemic mixtures and in the form of optically pure enantiomers in the pharmaceutical compositions that can be manufactured according to the invention.

The invention preferably relates to a process for the manufacture of pharmaceutical compositions in the form of aqueous dispersions containing unilamellar liposomes comprising (I) acid addition salts of antidepressants of the formula



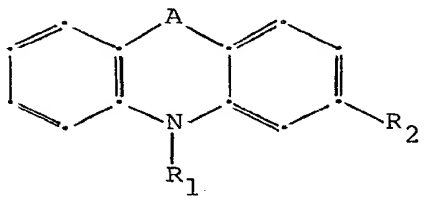
(1.8)

in which R_1 represents lower alkyl, for example methyl, R_2 represents lower alkylene, for example methylene, ethylene or 1,3-propylene, or hydroxy-lower alkylene, for example 2-hydroxy-1,3-propylene, and n represents 0 or 2; acid addition salts of anti-depressants of the formula



(1.9)

in which R_1 represents lower alkyl, for example methyl, A represents the group $N-R_1$, oxygen or sulphur, and R_2 represents hydrogen or cyano; acid addition salts of antidepressants of the formula



(1.10)

in which R_1 represents lower alkylamino-lower alkyl, for example 3-methylamino-n-propyl, di-lower alkylamino-lower alkyl, for example 3-dimethylamino-n-propyl, or 3-(4-(2-hydroxyethyl)-piperazin-1-yl)-n-propyl and A represents ethylene or vinylene; acid addition salts of psychoanaleptics, anoretics or adrenergics having a phenylaminopropane or cyclohexylaminopropane structure, for example amphetamine, methamphetamine, benzphetamine, propylhexedrine, prolintan, fencamfin, methylphenidate, pipradrol or phenmetrazine; acid addition salts of

spasmolytics, such as adiphenine; acid addition salts of sympathomimetics of the formula 1.5, for example epinephrine, norepinephrine, dopamine, nordefrin, ethylnorepinephrine, isoprenaline, isoethorine, metaproterenol, orciprenaline, metaraminol, phenylephrine, hydroxyamphetamine, methoxyphenamine, ephedrine, norephedrine, pholedrine, tyramine, norfenefrin or octopamine; ß-receptor blockers of the formula 1.6, for example acebutolol, atenolol, toliprolol, alprenolol, oxprenolol, bunitrolol, bupranolol, talinolol, phenbutolol, bufetolol or varbian (R,S-form and S-form); compounds having an action on peripheral noradrenaline storers, for example reserpine, rescinnamine or syringopine; glucocorticoids that are esterified in the 21-position by an amino acid, for example prednisolone diethylaminoacetate, or analgesically active phenylacetic acid salts, for example the sodium salts of diclofenac and pirprofen, and (II) a phospholipid of the formula 5 having two acyloxy radicals R_1 and R_2, for example lauroyloxy, myristoyloxy, palmitoyloxy, stearoyloxy, arachinoyloxy, oleoyloxy, linoyloxy or linoleoyloxy, for example natural lecithin (R_3 = hydrogen, R_4 = 2-trimethyl-ammonium ethyl) or natural cephalin (R_3 = hydrogen, R_4 = 2-ammonium ethyl) having different acyloxy radicals R_1 and R_2, for example egg lecithin or cephalin, or lecithin or cephalin from soya beans, synthetic lecithin or cephalin having different or identical acyloxy radicals R_1 and R_2, for example 1-palmitoyl-2-oleoyl lecithin or cephalin, or dipalmitoyl, distearoyl, diarachinoyl, dioleoyl, dilinoyl or dilinoleoyl lecithin or cephalin, natural phosphatidyl serine (R_3 = hydrogen, R_4 = 2-amino-2-carboxyethyl) having different acyloxy radicals R_1 and R_2, for example phosphatidyl serine from bovine

brain, synthetic phosphatidyl serine having different or identical acyloxy radicals R_1 and R_2, for example dioleoyl-, dimyristoyl- or dipalmitoyl-phosphatidyl serine, or natural phosphatidic acid (R_3 and R_4 = hydrogen) having different acyloxy radicals R_1 and R_2.

The invention relates especially to a process for the manufacture of pharmaceutical compositions in the form of aqueous dispersions containing unilamellar liposomes comprising (I) acid addition salts of antidepressants of the formula 1.8, for example 1-(2R-2-hydroxy-3-methylaminopropyl)-dibenzo[b,e]bicyclo-[2.2.2]octadiene, and the 2R,S-isomeric mixture, maprotiline, benzoctamine; acid addition salts of antidepressants of the formula 1.9, for example 3-methyl-dibenz[2,3:6,7]oxepino[4,5-d]azepine hydrochloride, 7-cyano-4-methyl-2,3,4,5-tetrahydro-1H-dibenzo[2,3:6,7]-thiepino[4,5-d]azepine ethanesulphonate, 3,10-dimethyl-1,2,3,4,5,10-hexahydrodibenzo[b,f]azepino[4,5]azepine maleate; acid addition salts of antidepressants of the formula 1.10, for example clomipramine, opipramol, desipramine or imipramine or imipramine N-oxide; acid addition salts of sympathomimetics of the formula 1.5, for example ephedrine or norephedrine; acid addition salts of ß-receptor blockers of the formula 1.6, for example 1-isopropylamino-3-[4-(2-methylthioethoxy)-phenoxy]-propan-2-ol, 1-isopropylamino-3-(2-pyrrol-1-ylphenoxy)-propan-2-ol, oxprenolol or prenalterol; spasmolytics, such as adiphenine, compounds having an action on peripheral noradrenaline storers, for example reserpine, glucocorticoids that are esterified in the 21-position by an amino acid, for example prednisolone diethylaminoacetate; analgesically active phenylacetic acid salts, for example the sodium salts of diclofenac and pirprofen, and (II) a phospholipid of

the formula 5, for example natural lecithin or cephalin, synthetic 1-palmitoyl-2-oleoyl lecithin or cephalin, dipalmitoyl, distearoyl, diarachinoyl, dioleoyl, dilinoyl or dilinoleoyl lecithin or cephalin, natural phosphatidyl serine, synthetic 1-palmitoyl-2-oleoylphosphatidyl serine, dimyristoyl- or dipalmitoyl-phosphatidyl serine or natural phosphatidic acid.

The manufacture of the homogeneous mixture of components can be effected in a manner known per se by film or lyophilisate formation. In film formation, the lipid, for example soya lecithin, and the biologically active compound, for example a pharmaceutical active ingredient, for example a sodium salt of diclofenac, are dissolved in an organic solvent. By removing the organic solvent, most advantageously in vacuo, preferably under a high vacuum, or by sweeping away with inert gas, for example nitrogen, a thin film of the components is prepared.

The choice of suitable solvents for the manufacture of the film is dependent upon the solubility of the lipid components and the inclusion compounds. Suitable solvents for the manufacture of the homogeneous mixture by film formation are, for example, unsubstituted or substituted, for example halogenated, aliphatic or cycloaliphatic hydrocarbons, for example n-hexane, cyclohexane, methylene chloride or chloroform, alcohols, for example methanol or ethanol, lower alkanecarboxylic acid esters, for example ethyl acetate, or ethers, for example diethyl ether, or mixtures of these solvents. The solvent is removed in vacuo, preferably under a high vacuum, or by sweeping away with inert gas, for example nitrogen.

The lyophilisate formation is effected by lyophilisation of a solution of the active ingredient

to be encapsulated and the lipid components in the manner described in DE-A 2 818 655. Suitable solvents are solid during freeze-drying, for example at the temperature of the methanol, ethanol or acetone drying mixture, together with the lipid components and the inclusion compounds, and are, for example, organic solvents having a melting point higher than 0°C, for example glacial acetic acid, benzene or dioxan, especially tert.-butanol.

A homogeneous mixture can also be prepared by spray-drying a solution of a cationic tenside, phospholipid and an inclusion compound in an organic solvent. The homogeneous mixture is obtained in the form of a powder.

In the homogeneous mixture, the approximate molar ratio of biologically active compound to lipid is approximately from 0.1 to approximately 2:1, preferably from approximately 0.8 to approximately 1.2:1.

Dispersion is effected, for example, by shaking (for example vortex mixer) or stirring the aqueous phase which contains the previously prepared homogeneous mixture. The formation of unilamellar liposomes (SUL) and (LUL) takes place spontaneously (spontaneous vesiculation), that is to say without the additional supply of external energy and at high speed. Approximately from 0.1 to 50% by weight, preferably approximately from 2 to 20% by weight (in relation to the total weight of the aqueous dispersion) of the homogeneous mixture can be dispersed in the aqueous phase.

Aqueous dispersions having a pH value greater than approximately 8 are neutralised after the dispersion operation, for example to the physiological pH value of 7.2. The neutralisation is necessary in order to avoid possible destruction of the active ingredient and/or

liposomes under basic conditions and in order to ensure physiological tolerability of the administrable aqueous dispersion with the liposome mixture. Neutralisation is effected, for example, with a physiologically tolerable, dilute aqueous solution of an acid or a buffer solution having a pH value of from 7 to 8. Physiologically tolerable acids are, for example, dilute aqueous mineral acids, for example dilute hydrochloric acid, sulphuric acid or phosphoric acid, or dilute organic acids, for example lower alkanecarboxylic acids, for example acetic acid.

Aqueous dispersions with amphiphatic compounds of the formula 1 can react acidically. These are neutralised by the addition of dilute aqueous bases, for example dilute aqueous sodium or potassium hydroxide solution or a buffer solution having a pH value of from 7 to 8, especially pH 7.2.

Aqueous dispersions with amphiphatic compounds of the formulae 2 and 4 can react basically. These are neutralised by the addition of a suitable physiologically tolerable acid, for example a weak organic acid, for example acetic acid, or a dilute aqueous mineral acid, for example dilute aqueous sulphuric acid. Neutralisation is carried out with simultaneous monitoring of the pH value.

The operations are advantageously carried out at room temperature or alternatively at higher temperatures, for example up to approximately 60°C, and while stirring or shaking. If the sensitivity of the active ingredient to be encapsulated demands, the process is carried out while cooling and optionally under an inert gas atmosphere, for example a nitrogen or argon atmosphere.

The size of the unilamellar liposomes formed depends, inter alia, on the structure of the active

ingredient and the lipid component, the mixing ratio of the components and the concentration of these components in the aqueous dispersion. Thus, for example, by increasing or reducing the concentration of the lipid component it is possible to produce aqueous phases having a high content of small or large unilamellar liposomes. In addition to SUL there are also formed large unilamellar liposomes (LUL-diameter up to 5.0×10^{-6}m) and, possibly, multilamellar liposomes.

The separation of the SUL from the LUL and any multilamellar liposomes formed as a secondary product, if desired, is effected by means of conventional separation methods, for example sedimentation of the LUL in an ultracentrifuge, gel filtration or extrusion through straight-pored filters. For example, on centrifuging, for example for from 5 to 30 minutes in a rotating field giving rise to an inertial force equivalent to a gravitational field of 5000-40 000 g, LUL are deposited, whilst the SUL remain dispersed and can be decanted off. After repeated centrifugation, complete separation of the LUL from the SUL is obtained.

It is also possible to separate off all the liposomes in the aqueous phase having a diameter greater than 6.0×10^{-8}m, for example LUL or multilamellar liposomes, as well as non-encapsulated active ingredients and excess dispersed lipids that are present in high-molecular-weight aggregates, by gel filtration, for example with Sepharose or Sephacryl as carriers and thus to obtain an aqueous phase having a fraction SUL of relatively uniform size.

By extrusion through straight-pored filters, for example membrane filters of the Nucleopore® type having a pore diameter of approximately 5.0×10^{-8}m,

at a pressure of approximately from 0.1 to 1.5 bar, and a filtration rate of approximately 20 ml/h, it is possible to obtain a particularly uniform size distribution of the unilamellar liposomes. The filtrate can subsequently be enriched with unilamellar liposomes by way of an ultrafilter, for example Amicon UM 10 ®.

The resulting liposomes are suitable for administration to patients and are stable in aqueous phase for a relatively long period (up to several days or weeks). Aqueous dispersions with the unilamellar liposomes that can be manufactured according to the invention can be made suitable for storage by the addition of stabilisers, for example mannitol or lactose.

The completed formation of small unilamellar liposomes (SUL) and their content in the aqueous phase can be detected in a manner known per se using various physical measuring methods, for example with freeze-fracture samples and thin sections in an electron microscope or by X-ray defraction, by dynamic light scattering, by mass determination of the filtrate in an analytical ultracentrifuge and, especially, by spectroscopy, for example in the nuclear resonance spectrum (^{1}H, ^{13}C and ^{31}P). For example, sharp signals having a narrow line width in the nuclear resonance spectrum indicate the completed formation of unilamellar liposomes of a diameter less than approximately 1000 Å. Sharp signals at δ approximately 0.89 ppm ($-CH_3$), δ approximately 1.28 ppm ($-CH_2-$) and δ approximately 3.23 ppm ($-N(CH_3)_3$) are characteristic, for example, of small unilamellar liposomes (vesicles) obtained according to the process with phosphatidyl choline (lecithin) as component. In the nuclear resonance spectrum such signals are typical

of unilamellar liposomes and differ markedly from signals caused by mixed micelles and large unilamellar and multilamellar liposomes. Large unilamellar and multilamellar liposomes with lecithin as component cause a broad coherent methyl and methylene signal of lesser intensity. A methyl signal of δ approximately 0.89 ppm is characteristic of mixed micelles with lecithin as component, which signal is resolved to a triplet and has a considerably smaller line width than the methyl signal (singlet, likewise at δ approximately 0.89 ppm) that originates from unilamellar liposomes.

Aqueous dispersions with the liposomes obtainable according to the invention and encapsulated active ingredients are administration systems which, optionally after concentration or isolation of the liposomes, for example by ultracentrifugation, are suitable for therapeutic purposes for oral (p.o.), parenteral (i.v., i.m. or i.p.) or topical administration.

In the case of oral administration, administration systems based on liposomes can improve the resorption of an active ingredient.

For oral administration, the liposome-containing aqueous dispersion can be mixed with pharmaceutically acceptable diluents or carriers or with customary additives, for example colourings or flavourings, or can be used in the form of a syrup or in the form of capsules.

For parenteral administration, the aqueous dispersion or the enriched liposomes can be suspended in a suitable carrier liquid, for example sterile, isotonic common salt or glucose solution, optionally buffered to pH 7.2.

For topical administration the liposome-containing aqueous dispersion can be mixed with customary thick-

eners, for example hydroxypropylcellulose, suitable preservatives, antioxidants and perfumes, and can be used in the form of a lotion or a gel for application to the skin or mucous membranes.

The dosage of active ingredient to be administered is generally the highest and lowest amount prescribed, for example in the Deutsches Arzneimittelbuch (DAB) [German Pharmacopoeia], for the active ingredient in question for the particular form of administration, the age of the patient and the health of the patient. Aqueous dispersions with liposomes that can be manufactured according to the invention also have the advantage, however, that active ingredients administered in smaller doses can pass to the receptors and can there bring about a therapeutic effect, or, on administration of higher doses, undesirable side effects can be avoided.

The active ingredients mentioned hereinbefore are known. Active ingredients of which the generic names are given are commercially available. The mentioned lipids, especially the phospholipids of the formula 5, are known and some are commercially available.

The following Examples illustrate the invention but do limit the invention. Temperatures are given in degrees Centigrade and chemical shifts in the NMR spectrum are given in ppm of standard tetramethylsilane. Unless otherwise indicated the signals are singlets. Sharp singlet signals at 1.26 - 1.32 ppm are characteristic of the methylene groups of the phospholipid of the formula 5 which is present in the aqueous dispersion in the form of small unilamellar liposomes. Phospholipids of the formula 5, which are present in the aqueous dispersion in the form of large unilamellar or multilamellar liposomes, have broad signals from approximately 0.5 to approximately 1.8

ppm. From the ratio of the intensities of the singlet signals of the methylene groups of the lipid and the standard sodium acetate it is possible to calculate the yield of small unilamellar liposomes (SUL). Sterile water that has been washed free of particles is used for preparing the aqueous dispersions.

Example 1

1.1 50 mg (approximately 0.066 mmol) of soya lecithin are weighed into a 15 ml phial, and a solution of 20.33 mg (0.066 mmol) of 1-isopropylamino-3-(2-pyrrol-1-ylphenoxy)-propan-2-ol hydrochloride in 3 ml of a 1:1 methanol/chloroform mixture is added thereto. After the lecithin has been dissolved in the organic phase, the phial, in a horizontal position, is set rapidly in rotation until a film of liquid adheres to the glass wall. The solvent is removed by sweeping it away with nitrogen and the lipid film that has formed is dried under a high vacuum for several hours.

1.2 1.5 ml of water or (if it is intended to record an ^{1}H-NMR spectrum) D_2O are then added to this lipid film and the phial is shaken for several minutes, optionally mechanically and at high speed (vortex mixer). A slightly opalescent, aqueous dispersion is obtained.

The completed formation of small, unilamellar liposomes (SUL) can be detected in the ^{1}H-NMR spectrum (360 MHz) inter alia by a sharp singlet signal at 0.53 ppm which is characteristic of the methyl groups of the lipid soya lecithin. The spectrum also shows in the range of from 0.53 to 1.63 ppm a broad signal of lesser intensity, which is assigned to the methyl and methylene groups of the soya lecithin contained in large unilamellar and multilamellar liposomes. In addition to other signals, the doublet at 1.26, which is assigned to the $-CH(CH_3)_2$ group of the active ingredient, is characteristic. Yield of SUL: 23.4%.

The unilamellar liposomes formed can be observed in an electron microscope. The liposome dispersion is

first subjected to the customary freeze-fracture method. There are chiefly two "populations" of unilamellar liposomes present which differ in their average size:

1. Small unilamellar liposomes (SUL) having a diameter of approximately 2.0-6.0 x 10^{-8}m, and

2. Large unilamellar liposomes (LUL) having a diameter of approximately 1.0 x 10^{-7} - 1.0 x 10^{-6}m.

Example 2

In a manner analogous to that described in Example 1.1, a lipid film is prepared from 50 mg (approximately 0.066 mmol) of soya lecithin and an equimolar amount of the following active ingredients, and the film is dispersed analogously to Example 1.2 in 2.5 ml of water or D_2O. The ^{1}H-NMR spectra show sharp singlets for the methyl and methylene groups of the lecithin present in the form of SUL and a broad signal of lesser intensity for the methyl and methylene groups of the lecithin present in the form of LUL and multilamellar liposomes. In addition, the signals characteristic of the particular active ingredient can be detected.

2.1 21.15 mg of 1-(2R-2-hydroxy-3-methylaminopropyl)-dibenzo[b,e]bicyclo[2.2.2]octadiene hydrochloride (NMR: 3.30 -$NHCH_3$), yield SUL: 12.4%.

2.2 21.15 mg of 1-(2R,S-2-hydroxy-3-methylamino-propyl)-dibenzo[b,e]bicyclo[2.2.2]octadiene hydro-chloride (NMR: 3.26 -$NHCH_3$), yield SUL: 22.0%.

2.3 20.06 mg of 3-methyldibenzo[2,3:6,7]oxepino-

[4,5-d]azepine hydrochloride (NMR: 3.19 $-NCH_3$), yield SUL: 26%.

2.4 25.48 mg of 2,3,4,5-tetrahydro-3-methyl-1H-dibenzo[2,3:6,7]thiepino[4,5-d)azepine-7-cyanomethane-sulphonate (NMR: 3.14 $-NCH_3$), yield SUL: 29.5%.

2.5 26.80 mg of 3,10-dimethyl-1,2,3,4,5,10-hexahydro-dibenzo[b,f]azepino[4,5]azepine maleate (NMR: 1.38 $-CH(\underline{CH_3}_2$-doublet, 2.19 $-SCH_3$), yield SUL: 25%.

2.6 46.99 mg of 1-isopropylamino-3-[4-(2-methylthio-ethoxy)-phenoxy]-propan-2-ol fumarate (NMR: 1.38 $-CH(\underline{CH_3}_2$-doublet, 2.19 $-SCH_3$), yield SUL: 25%.

2.7 20.262 mg of N,N-dimethyl-5-phenyl-1,2,4-triazolo-[1,5-a]quinoxalin-2-ylmethylamine hydrochloride (NMR: 3.04 $-NCH_3$, 2.91 $-N(CH_3)_2$), yield SUL: 21.2%.

2.8 21.12 mg of clomipramine hydrochloride (NMR: 3.20 $-N(CH_3)_2$), yield SUL: 29%.

2.9 13.21 mg of ephedrine hydrochloride (NMR: 2.77 $-NHCH_3$), yield SUL: 18%.

2.10 26.33 mg of opipramol (NMR: 7.10 -CH=CH-multiplet), yield SUL: 26%.

2.11 20.65 mg of maprotiline hydrochloride (NMR: 3.17 $-NHCH_3$), yield SUL: 15.1%.

2.12 12.38 mg of phenylpropanolamine hydrochloride (norephedrine hydrochloride, NMR: 1.19 $-NCH_3$), yield

SUL: 10.8%.

2.13 42.81 mg of oxprenolol succinate (NMR: 1.30 $-CH_3$-doublet), yield SUL: 24%.

2.14 19.92 mg of desipramine hydrochoride (NMR: 6.77 - 7.44, multiplet-arom. H), yield SUL: 17.7%.

2.15 20.91 mg of phentolamine hydrochloride (NMR: 2.30 $-C_6H_5-\underline{CH_3}$), yield SUL: 12.2%.

2.16 18.80 mg of benzobutamine hydrochloride (NMR: 3.67 $-NCH_3$), yield SUL: 10.2%.

2.17 20.84 mg of imipramine hydrochloride (NMR: 3.07 $-NCH_3$), yield SUL: 24.1%.

2.18 22.96 mg of adiphenine hydrochloride (NMR: 2.00 $-COOCH_2-$), yield SUL: 56%.

2.19 30.08 mg of oxprenolol hydrochloride (NMR: 1.33 $-CH_3$-doublet), yield SUL: 16%.

2.20 17.19 mg of prenalterol hydrochloride (NMR: 1.33 $-CH_3$-doublet , 6.87 arom. H-multiplet), yield SUL: 16%.

2.21 18.67 mg of diclofenac sodium (NMR: 3.00 $-CH_2-$), yield SUL: 16%.

2.22 17.74 mg of methylphenidate hydrochloride (NMR: 3.73 $-COOCH_3$), yield SUL: 10.3%.

Example 3

3.1 23.26 mg (approximately 0.066 mmol) of cefroxadin are dissolved in 5 ml of a 2:1 dioxan/methanol mixture in the presence of slight traces of water. 50 mg (approximately 0.066 mmol) of soya lecithin are dissolved in the clear solution. The solvent is removed in vacuo at 50°. The lipid film that has formed is dried under a high vacuum for several hours.

3.2 2.5 ml of water or (if it is intended to record an ^{1}H-NMR spectrum) D_2O are then added to this film and the whole is shaken for several minutes, optionally mechanically and at high speed. After the addition of a drop of a 1% solution of bromothymol blue in D_2O, titration is carried out with a few drops of a 1N NaOH or NaOD/D_2O solution to produce a colour change from yellow to blue (pH approximately 9-10). After several minutes' mechanical stirring, the dispersion is neutralised with 1N H_2SO_4 or D_2SO_4/D_2O solution (colour change from blue to yellow). A slightly opalescent, aqueous dispersion is obtained. In the NMR spectrum, in addition to the methyl and methylene signals that are characteristic of the lipid, and other signals, a singlet can be detected at 3.73 ppm which is assigned to the OCH_3 group of cefroxadin. Yield SUL: 13.2%.

Example 4

4.1 50 mg (approximately 0.066 mmol) of soya lecithin are weighed into a 15 ml phial, and a solution of 16.53 mg (0.066 mmol) of pirprofen in 3 ml of a 1:1 methanol/chloroform mixture is added thereto. After the lecithin has been dissolved in the organic phase,

the phial is set rapidly in rotation until a film of liquid adheres to the glass wall. The solvent is removed by sweeping it away with nitrogen and the lipid film that has formed is dried under a high vacuum for several hours.

4.2 2.5 ml of water or (if it is intended to record an ^{1}H-NMR spectrum) D_2O are then added to this lipid film and the whole is shaken, optionally mechanically, for several minutes. After the addition of a drop of bromothymol blue in D_2O, titration is carried out with a few drops of a 1N NaOD/D_2O solution to produce a colour change from yellow to blue (pH approximately 9-10). After several minutes' mechanical stirring, the dispersion is neutralised with 1N H_2SO_4 or D_2SO_4/D_2O solution (colour change from blue to yellow). A slightly opalescent, aqueous dispersion is obtained. In the NMR spectrum, in addition to the methyl and methylene signals that are characteristic of the phospholipid and in addition to other signals, a broad singlet can be detected at 6.04 ppm which is assigned to the vinyl protons in the pirprofen. Yield SUL: approximately 11.6%.

Example 5

5.1 In a manner analogous to that described in Example 4.1, a film of liquid is prepared from 50 mg (approximately 0.066 mmol) of soya lecithin and 40.17 mg (0.066 mmol) of reserpine and is subsequently dried under a high vacuum.

5.2 25 ml of water or (if it is intended to record an ^{1}H-NMR spectrum) D_2O are then added to this film and the whole is shaken for several minutes, optionally mechanically and at high speed. After the addition of

a drop of a 0.5% solution of bromophenol blue in D_2O, titration is carried out with a few drops of a 1N H_2SO_4 or D_2SO_4/D_2O solution to produce a colour change from blue to yellow (pH approximately 3). After several minutes' mechanical stirring, the dispersion is neutralised with 1N NaOH or $NaOD/D_2O$ solution. A slightly opalescent, aqueous phase is obtained. In the NMR spectrum, in addition to the methyl and methylene signals characteristic of the lipid and other signals, a singlet can be detected at 3.81 ppm which is assigned to the $-OCH_3$ groups at the phenyl ring of the reserpine.

Example 6

6.1 In a manner analogous to that described in Example 4.1, a film of liquid is prepared from 50 mg (approximately 0.066 mmol) of soya lecithin and 31.26 mg (approximately 0.066 mmol) of prednisolone diethylaminoacetate and is then dried under a high vacuum.

6.2 An aqueous dispersion having unilamellar liposomes is then prepared from this film analogously to Example 5.1. In the NMR spectrum, in addition to the methyl and methylene signals characteristic of the lipid and other signals, a singlet can be detected at 7.66 ppm which is assigned to the vinylic proton of the prednisolone nucleus that is in the α-position to the carbonyl group.

Example 7

7.1 2.9 g (3.88 mmol) of soya lecithin are dissolved in 20 ml of tert.-butanol at approximately 50°. At this temperature, while stirring, 2 ml of water are

added dropwise and then 2 g (3.88 mmol) of beta-methasone disodium phosphate are dissolved in the solution. The clear solution is frozen at -30° and freeze-dried at this temperature.

7.2 2.5 ml of water are added to the resulting lyophilisate and the whole is mechanically shaken for 5 minutes. A slightly opalescent, aqueous dispersion having unilamellar liposomes is obtained. In the ^{1}H-NMR spectrum it is possible to detect the methylene and methyl signals of the lipid and, inter alia, a doublet at 7.49 (J = 9 Hz, 1-H atom at the steroid nucleus), doublet at 6.38 (J = 9 Hz, 2-H atom) and a singlet at 6.19 (4-H atom). Yield SUL : 44%.

7.3 The resulting aqueous dispersion is adjusted to pH 7.4 by the addition of sterile 0.1N hydrochloric acid. After introduction into a stirred ultrafiltration cell (Amicon®), which instead of the ultrafilter is provided with a straight-pored membrane filter of polycarbonate (Nucleopore®) having a pore diameter of 0.05 µm and which has been washed free of particles, filtration is carried out under a slight excess pressure of approximately from 0.1 to 1.5 bar and with a constant supply of sterile-filtered buffer solution according to Dulbecco (pH 7.4, without Ca and Mg) at a speed of 20 ml/h, until approximately 500 ml of filtrate have been obtained. This filtrate is fed continuously into a stirred filtration cell equipped with an ultrafilter, for example Amicon U 10®, and concentrated to a volume of 30 ml. The concentrated aqueous dispersion contains small, unilamellar liposomes and, after the addition of a concentrate of phosphate buffer according to Dulbecco (pH 7.4 without Ca and Mg), can be introduced into ampoules and used

for treatment tests.

7.4 In a manner analogous to that described in Example 7.3, it is possible to manufacture by membrane filtration and subsequent ultrafiltration concentrated aqueous dispersions containing small unilamellar liposomes with the compositions indicated in Examples 1 to 6 and 8.

Example 8

8.1 In a manner analogous to that described in Example 7.1, a lyophilisate is manufactured from 3.21 g (4.22 mmol) of soya lecithin and 2 g (4.22 mmol) of prednisolone diethylaminoacetate.

8.2 In a manner analogous to that described in Example 7.2, the resulting lyophilisate is dispersed in water, and a slightly opalescent, aqueous dispersion having unilamellar liposomes is obtained. In the ^{1}H-NMR spectrum it is possible to detect the methyl and methylene signals of the lipid and, inter alia, a broad signal at 6.31 (2-H atom at the steroid nucleus) and a singlet at 6.06 (4-H atom). Yield SUL: 14.4%.

Example 9 (Anti-inflammatory steroid injection preparation)

29 g of 1-palmitoyl-2-oleoyl lecithin are dissolved in 450 ml of tert.-butanol at 50°. While stirring, 20 ml of distilled water and 20 g of beta-methasone disodium phosphate are added to this solution. In a sterile room, the resulting solution is filtered through a sterile filter (for example Acrodisc 0.2 µm) into a sterile flask washed free of particles

and having a pipette metering attachment. 0.1 ml portions of this solution (corresponding to 4 mg of active ingredient) are introduced into washed, sterile 2 ml phials, lyophilised under sterile conditions and sealed under dry nitrogen. The resulting dry preparation is stable to storage. Before use, 1 ml of sterile, phosphate-buffered (pH 7.4) common salt solution is added to this dry preparation using a sterile syringe and the phials are shaken for 1 minute in a standardised laboratory shaker (vortex, Stage 6). The resulting liposome dispersion is suitable for intramuscular, intra-articular, intradermal or intralesional injection.

Example 10 (Steroid cream)

29 g of soya lecithin (Epikuron 200 ®) are dissolved in 200 ml of tert.-butanol at 50°. At this temperature, while stirring, 20 ml of distilled water and 20 mg of betamethasone disodium phosphate are added. The solution is frozen, lyophilised and ground at low temperature under a nitrogen atmosphere (dry). The lyophilisate is stirred in a stirring vessel for a period of 10 minutes in 5 kg of distilled water. In a Moltomat an aqueous gel is prepared from 14.4 kg of water, 300 g of Klucel and 200 g of sodium ascorbate and customary perfumes and preservative additives in a manner known per se, and the liposome mixture is mixed in. The resulting cream is suitable for the treatment of weeping dermatoses.

Example 11 (Antirheumatic agent for peroral administration)

1 kg of soya lecithin (Epikuron 200 ®) is

dissolved in 5 litres of tert.-butanol at 50°. At this temperature 250 ml of water and 250 g of diclofenac sodium are added. The solution is lyophilised and the lyophilisate is finely ground under a nitrogen atmosphere (dry) in a pinned disk mill and then mixed in a Turbula mixer with 2.5 kg of ground lactose, 5 g of sodium ascorbate and flavour-correctors. 750 mg portions of the pulverulent mixture are sealed into composite foil bags (polyethylene/-aluminium/paper). Before administration, the contents of the bag are stirred in a glass of water (1 dl), a liposome dispersion for drinking being formed.

Example 12 (Eye drops against conjunctivitis)

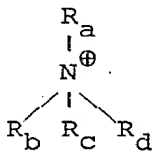
20 g of 1-palmitoyl-2-oleoyl lecithin are dissolved in 400 ml of tert.-butanol. 40 ml of distilled water and 2 g of diclofenac sodium are added. The solution is filtered in a sterile room through a sterile filter (for example Acrodisc 0.2 µm) into a sterile flask washed free of particles and having a pipette attachment. 1 ml portions of this solution (corresponding to 50 mg of phospholipid) are introduced into washed, sterile 50 ml phials, frozen at -70°, sterile-lyophilised and sealed under dry nitrogen. The resulting dry preparation is stable to storage. Before use, 2.5 ml of sterile, phosphate-buffered common salt solution (according to Dulbecco, Ca- and Mg-free, pH 7.4) are added to the dry preparation and the phials are shaken vigorously for approximately 20 seconds. The resulting suspension can be stored for 1 month in a refrigerator if kept sealed. For treatment, 1 or 2 drops are applied to each eye daily.

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. Process for the manufacture of pharmaceutical compositions in the form of aqueous dispersions containing unilamellar liposomes comprising (I) an amphiphatic compound having biological activity and (II) a phospholipid or an analogous lipid and, optionally, an additional lipid, characterized in that (I) the amphiphatic compound having biological activity and (II) the phospholipid or the analogous lipid and, optionally, the additional lipid are homogeneously mixed and the resulting homogeneous mixture is dispersed in an aqueous phase and the resulting aqueous dispersion is neutralised.

2. Process according to claim 1, characterised in that there are homogeneously mixed and dispersed (I), as the amphiphatic compound having biological activity,

a substituted ammonium compound of the formula



(1)

in which

a) R_a represents a hydrophobic group, and R_b, R_c and R_d, independently of one another, each represents hydrogen, C_1-C_4-alkyl, 2-hydroxyethyl, allyl or cyclo-C_3-C_6-alkyl-C_1-C_3-alkyl, or two of the radicals R_b, R_c and R_d together represent C_4- or C_5- alkylene or such group interrupted by -HN-, -N(C_1-C_4-

alkyl)-, -N(2-hydroxyethyl)- or by oxygen, or

b) R_a and R_b are two hydrophobic groups or together represent a hydrophobic group, and R_c and R_d, independently of one another, each represents hydrogen, C_1-C_4-alkyl, allyl or cyclo-C_3-C_6-alkyl-C_1-C_3-alkyl, or

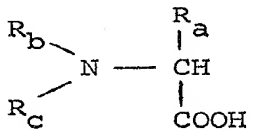
c) R_a, R_b and R_c together represent a hydrophobic group, and R_d represents hydrogen or C_1-C_4-alkyl, and $X^{\ominus}$ represents the anion of a pharmaceutically acceptable acid,

a carboxylic acid salt of the formula

$$R_a\text{-}COO^{\ominus}\ Y^{\oplus} \qquad (2)$$

in which R_a represents a hydrophobic group, and $Y^{\oplus}$ represents the cation of a pharmaceutically acceptable base,

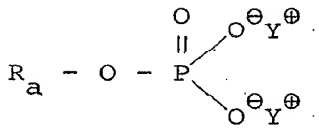
an α-amino acid compound of the formula



(3)

in which R_a represents a hydrophobic group, and R_b and R_c, independently of one another, each represents hydrogen or C_1-C_4-alkyl,

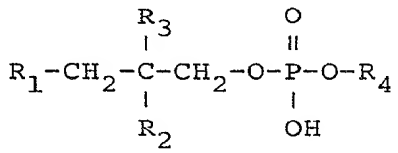
a phosphoric acid monoester of the formula



(4)

in which R_a represents a hydrophobic group and $Y^{\oplus}$ represents the cation of a pharmaceutically acceptable base, or

an acid addition salt of a compound having a hydrophobic group R_a and an imidazoline, imidazolidine or hydrazino group as hydrophilic group, and (II), as the phospholipid, a compound of the formula

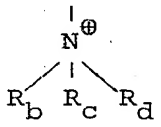


(5)

in which one of the radicals R_1 and R_2 represents hydrogen, hydroxy or C_1-C_4-alkyl, and the other radical represents alkyl, alkenyl, alkoxy, alkenyloxy or acyloxy each having from 10 to 20 carbon atoms, or both radicals R_1 and R_2 represent alkyl, alkenyl, alkoxy, alkenyloxy or acyloxy each having from 10 to 20 carbon atoms, R_3 represents hydrogen or C_1-C_4-alkyl, and R_4 represents hydrogen, C_1-C_7-alkyl, substituted C_1-C_7-alkyl or a carbohydrate radical having from 5 to 12 carbon atoms or, if both radicals

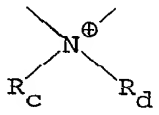
R_1 and R_2 represent hydrogen or hydroxy, R_4 represents a steroid radical, or is a salt thereof.

3. Process according to claim 2, characterised in that there are homogeneously mixed and dispersed (I) a substituted ammonium compound of the formula 1 in which
a) the hydrophobic group can be an aliphatic hydrocarbon radical that can be interrupted by an oxygen or sulphur atom, may contain the groups -CO(=O)-, -O-C(=O)-, -C(=O)-NH-, -O-C(=O)-NH- or hydroxy, and can be substituted by from 1 to 3 monocyclic, aliphatic or aromatic hydrocarbon radicals, by a bi- or tri-cyclic, aromatic or partially saturated hydrocarbon radical, by a monocyclic, aromatic, partially saturated or saturated heterocycle or by a bi- or tri-cyclic, aromatic, partially saturated or benzo-fused heterocycle, or can be a monocyclic, aliphatic or aromatic hydrocarbon radical or a bicyclic, aliphatic or benzo-fused hydrocarbon radical, and the hydrophilic group is a group of the formula



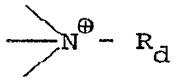
in which R_b, R_c and R_d, independently of one another, each represents hydrogen, C_1-C_4-alkyl or 2-hydroxyethyl, or in which two of the radicals R_b, R_c and R_d together represent piperidino, piperazinyl, 1-methylpiperazinyl, 1-(2-hydroxyethyl)-piperazinyl or morpholino, and the other radical represents hydrogen, or

b) the hydrophobic groups R_a and R_b can be two aliphatic hydrocarbon radicals which can be substituted by one or two monocyclic, aliphatic or aromatic hydrocarbon radicals or by substituted, monocyclic, aromatic, partially saturated or saturated heterocycle, or R_a and R_b together represent a monocyclic, aromatic, saturated, partially saturated or benzo-fused heterocycle, and the hydrophilic group is a group of the formula



in which R_c and R_d, independently of one another, each represents hydrogen or C_1-D_4-alkyl, or

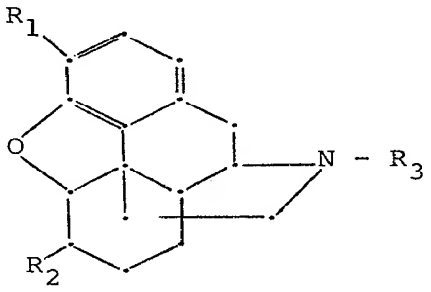
c) the hydrophobic group is formed by R_a, R_b and R_c together and represents an aromatic, partially saturated or benzo-fused heterocycle and the hydrophilic group is a group of the formula



in which R_d represents hydrogen or C_1-C_4-alkyl, and $X^{\ominus}$ is the anion of a pharmaceutically acceptable acid, or a carboxylic acid salt of the formula 2 in which the hydrophobic group R_a can be an aliphatic hydrocarbon radical which can be substituted by a monocyclic, aromatic hydrocarbon radical or by a bi- or tri-cyclic, aromatic or partially saturated hydrocarbon radical, by a monocyclic, aromatic or partially saturated heterocycle or by a bi- or tri-cyclic, aromatic, partially saturated or benzo-fused heterocycle or by a steroid radical, or R_a can be a monocyclic, aromatic hydrocarbon radical, a bi- or tri-cyclic, aromatic or partially saturated hydrocarbon radical, a monocyclic, aromatic or partially saturated heterocycle or a bi- or tri-cyclic, aromatic, partially saturated or benzo-fused heterocycle, and $Y^{\oplus}$ is the cation of a pharmaceutically acceptable base, and (II), as the phospholipid, a compound of the formula 5 in which both radicals R_1 and R_2 represent alkyl, alkenyl, alkoxy, alkenyloxy or acyloxy each having from 10 to 20 carbon atoms, R_3 represents hydrogen or C_1-C_4- alkyl, and R_4 represents hydrogen or C_1-C_4-alkyl, and R_4 represents hydrogen, C_1-C_7-alkyl or substituted C_1-C_7-alkyl or a carbohydrate radical having from 5 to 12 carbon atoms, or a salt thereof.

4. Process according to claim 2,
characterised in that there are homogeneously mixed and dispersed (I), as the substituted ammonium compound or as the corresponding amino compound that can be converted into the ammonium compound by salt formation,

a compound selected from the group comprising parasympathomimetics having quaternary or tertiary amino groups, choline esterase inhibitors having two tertiary amino groups or having a quaternary ammonium group, neurotransmitters having a quaternary ammonium group, serotonin-antagonists in which the hydrophilic group is a primary or tertiary amino group and the hydrophobic group has an indol-3-ylethyl structure, analgesics of the morphine type having a tertiary amino group and their antagonists of the formula



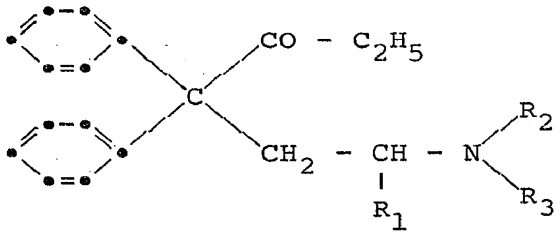
(1.1)

in which R_1, R_2 and R_3 have the following meanings:

R_1	R_2	R_3	Name
-OH	-OH	$-CH_3$	Morphine
-OH	=O	$-CH_3$	Hydromorphone
-OH	=O	$-CH_3$	Oxymorphone
-OH	-H	$-CH_3$	Levorphanol
$-OCH_3$	-OH	$-CH_3$	Codeine
$-OCH_3$	=O	$-CH_3$	Hydrocodone
$-OCH_3$	=O	$-CH_3$	Oxycodone
-OH	-OH	allyl	Nalorphine

R_1	R_2	R_3	name
-OH	=O	allyl	Naloxone
-OH	=O	cyclopropylmethyl	Naltrexone
-OH	$-OCH_3$	cyclopropylmethyl	Buprenophine
-OH	-H	cyclobutylmethyl	Butorphanol
-OH	-OH	cyclobutylmethyl	Nalbuphine
-2-(morpholin-1-yl)-ethyl)	-OH	$-CH_3$	Pholcodine,

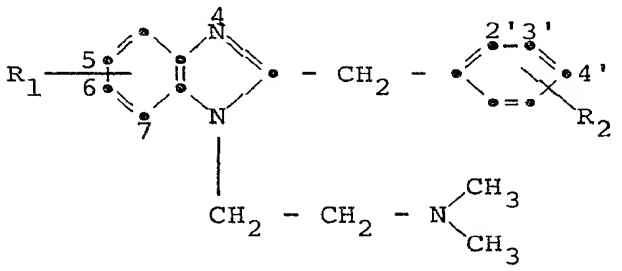
analgesics of the benzomorphan type having a tertiary amino group, analgesics of the pethidine type, analgesics of the methadone type in which the hydrophobic group is a 1,1-diphenyl-1-lower alkyl-2-butanone radical and the hydrophilic group is dimethylamino, morpholino or piperidino of the formula



(1.2)

in which R_1 represents hydrogen or methyl, R_2 and R_3 each represents methyl, or R_2 and R_3 together represent morpholino or piperidino, or analogues thereof having a pseudomethadone structure, analgesics

similar to morphine having an aliphatic or cycloaliphatic tertiary amino group, analgesics of the benzimidazole type of the formula

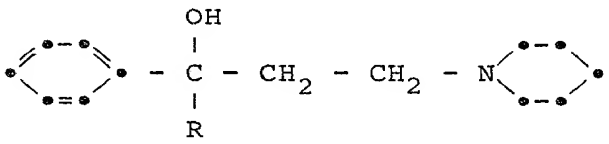


(1.3)

in which R_1 represents 5-, 6- or 7-nitro, R_2 represents hydrogen, 3'- or 4'-methoxy, 4'-ethoxy, 4'-isopropoxy, 4'-methyl or 4'-chloro, local anaesthetics in which R_a and R_b in the formula 1 together with the nitrogen atom form a piperidyl radical that is substituted by a 1,3-propylene, that is itself substituted by a methoxycarbonyl and benzoyloxy group, local anaesthetics in which the hydrophobic group R_a in the formula (1) is a 4-aminobenzoyloxyethyl, 4-amino-2-chloro-, 2-n-butoxy- or 2-hydroxy-benzoyloxyethyl, 4-amino-3-n-butoxybenzoyloxyethyl, 3-amino-4-n-butoxy-benzoyloxyethyl, 2-aminobenzoyloxyethyl, 2-(4-aminobenzoyloxy)-6-methyl-n-pentyl, 4-aminobenzoyloxy-n-propyl, 4-n-butylaminobenzoyloxyethyl, 4-n-butyl-2-hydroxybenzoyloxyethyl, 3-(4-n-propoxybenzoyloxy-2-hydroxy)-propyl, 2-n-benzoyloxy-n-propyl, 2-(2-acetoxybenzoyloxy)-n-propyl, benzoyloxy-n-propyl, 4-cyclohexyloxybenzoyloxyethyl, 4-ethyl- or 4-n-butyl-benzoyloxyethyl, 2-n-butoxyquinol-4-ylcarbonyloxyethyl, 2,4-dimethylanilinocarbonylmethyl, 2-ethyl-, 2-chloro-

or 2-methoxycarbonylmethyl-4-methylanilinocarbonylmethyl, 1-(2-methylanilinocarbonyl)-ethyl, (2-ethoxycarbonyl-4-methylthien-3-ylaminocarbonyl)-ethyl, 2,3-dianilinocarbonyloxypropyl, 4-n-propyl- or 4-n-butylbenzoylethyl, 4-phenoxymethylphenyl-n-butyl, 4-n-butoxyphenoxy-n-propyl, 2-n-butylquinol-8-yloxymethyl or 8-benzoyloxycarbonyl-1,2,3,4-tetrahydronaphth-2-yl group, and the hydrophilic group is lower alkylamino, cyclohexylamino, 1-methylpiperid-2-yl, piperid-1- or -2-yl or morpholin-1-yl, neuroleptics or thymoleptics in which the nonpolar, hydrophobic group R_a in the formula 1 is lower alkyl or hydroxy-lower alkyl that is substituted by 2-cyano-, 2-methoxy-, 2-chloro-, 2-trifluoromethyl-, 2-methylthio-, 2-acetyl- or 2-ethyl-10H-phenothiazin-10-yl, 9H-acridin-10-yl, 5H-dibenzo[b,f]azepin--5-yl, 7-chloro-10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl, 5, 10-dihydro-5-methyl-11-dibenzo[b,e]-1,4-diazepin-11-onyl, 2-chloro-, 2-trifluoromethyl- or 2-dimethyl-aminosulphonyl-9H-thioxanthen-9-ylidene, 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl or by 10H-pyrido[3,2-b]-[1,4]benzothiazin-10-yl, and the polar, hydrophilic group represents amino, lower alkylamino, di-lower alkylamino, tri-lower alkylamino, piperidino or 4-hydroxyethyl-piperazino, antidepressants having a tertiary amino group, thymeretics having a primary or methyl- and propargyl-substituted tertiary amino group,
sedatives in which the hydrophobic group R_a in the formula 1 is the 2-(7-chloro-5-o-fluorophenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-on-1-yl)-ethyl radical and the hydrophilic group is diethylamino, psychodysleptics having a β-phenylethylamine structure, psychodysleptics in which the

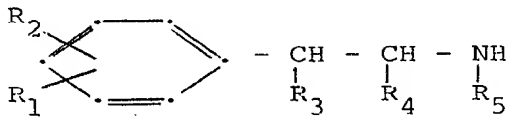
hydrophobic group R_a in the formula 1 is an ethyl radical substituted by a 3-indole radical, psychodysleptics in which R_a and R_b in the formula 1 together with the nitrogen atom form a morpholine or pyrrolidine ring that is substituted by 1,3-lower alkylene, anticholinergics having an atropine structure, anticholinergics (agents against Parkinson's Disease) of the formula



(1.4)

in which R represents cyclohexyl, cyclopentyl, phenyl or norborn-5-en-2-yl, and analogues, anticholinergics having a tertiary amino group, central analeptics having a morpholine group, psychoanaleptics having a 4-chlorophenoxyacetoxyethyl group as hydrophobic group and a dimethylamino group as hydrophilic group, vasodilatators having a tertiary amino group, appetite suppressants having an amphetamine structure, muscle relaxants having a hydrophobic group and several quaternary amino groups, neurotropic spasmolytics having quaternary amino groups, musculotropic spasmolytics having tertiary amino groups, 4-aminoquinoline antirheumatics, anti-oestrogens having a

tertiary amino group, histamine H_1-receptor antagonists (antihistamines) having an ethylenediamine group, a 2-aminoethanol group or a 3-aminopropane group, sympathomimetics of the formula



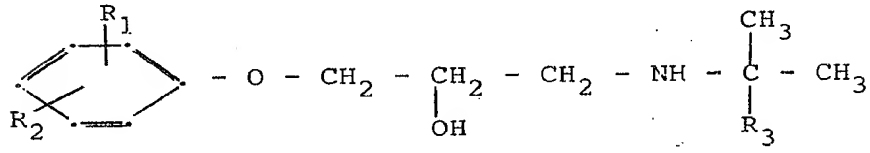
(1.5)

in which R_1, R_2, R_3, R_4 and R_5 have the following meanings:

R_1	R_2	R_3	R_4	R_5	Name
3-OH	4-OH	-OH	-H	$-CH_3$	Epinephrine (Adrenaline)
3-OH	4-OH	-OH	-H	-H	Norepinephrine (Noradrenaline)
3-OH	4-OH	-H	-H	-H	Dopamine
3-OH	4-OH	-OH	$-CH_3$	-H	Nordefrin
3-OH	4-OH	-OH	$-C_2H_5$	-H	Ethylnorepine-phrine
3-OH	4-OH	-OH	-H	$-CH(CH_3)_2$	Isoprenaline
3-OH	4-OH	-OH	$-C_2H_5$	$-CH(CH_3)_2$	Isoethorine
3-OH	4-OH	-OH	-H	$-CH(CH_3)_2$	Metaproterenol
3-OH	5-OH	-OH	-H	$-C(CH_3)_3$	Orciprenaline
3-OH	-H	-OH	$-CH_3$	-H	Metaraminol
3-OH	-H	-OH	-H	$-CH_3$	Phenylephrine

R_1	R_2	R_3	R_4	R_5	Name
4-OH	-H	-H	-H	-H	Hydroxy-amphetamine
2-OCH_3	-H	-H	$-CH_3$	$-CH_3$	Methoxy-phenamine
2-OCH_3	5-OCH_3	-OH	$-CH_3$	-H	Methoxamine
3-CH_2OH	4-OH	-OH	-H	$-C(CH_3)_3$	Albuterol
-H	-H	-OH	$-CH_3$	$-CH_3$	Ephedrine
-H	-H	-OH	$-CH_3$	-H	Norephedrine
3-CF_3	-H	-H	$-CH_3$	$-C_2H_5$	Fenfluramine
-H	-H	-OH	$-CH_3$	-H	Phenylpropanol-amine
4-OH	-H	-OH	$-CH_3$	$-CH_3$	Pholedrine
4-OH	-H	-OH	$-CH_3$	-H	Tyramine
3-Cl	4-Cl	-OH	-H	$-C(CH_3)_3$	Dichloro-isoprenaline
4-OH	-H	-OH	-H	$-CH_3$	Norfenefrine
4-OH	-H	-OH	-H	-H	Octopamine
3-OH	-H	-OH	-H	$-C_2H_5$	Etilefrin,

β-receptor blockers of the formula:

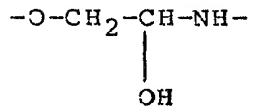


(1.6)

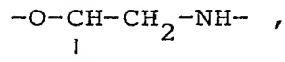
in which R_1, R_2 and R_3 have the following meanings:

R_1	R_2	R_3	Name
2-acetyl	4-n-butyryl-amino	H	Acebutolol
4-carbamoylmethyl	H	H	Atenolol
4-(2-carbamoylethyl)	H	H	Metoprolol
3-methyl	H	H	Toliprolol
2-allyl	H	H	Alprenolol
2-allyloxy	H	H	Oxprenolol
2-cyano	H	methyl	Bunitrolol
2-chloro	5-methyl	methyl	Bupranolol
3-(N-cyclohexyl-N'-ureido)	H	methyl	Talinolol
2-cyclopentyl	H	methyl	Phenbutolol
2-tetrahydrofur-2-ylmethoxy	H	methyl	Bufetolol
2-pyrrol-1-yl	H	H	
4-(2-methylthio-ethoxy)	H	H	
4-OH	H	H	Varbian, R,S-form, S-form,

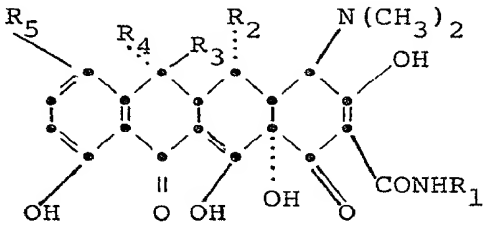
β-blockers having as hydrophobic group the naphthyloxy, indolyloxy, 2-methylindolyloxy, 1,2,3,4-tetrahydronaphth-2,3-diol-1-yl or 1,2,3,4-tetrahydronaphth-5-on-1-yl radical, β-blockers in which the segment



has been replaced by



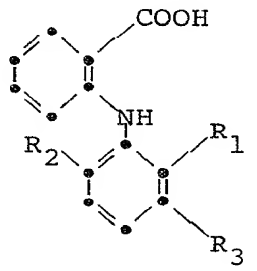
compounds of the reserpine type, tetracycline antibiotics of the formula



(1.7)

in which R_1 represents hydrogen or pyrrolidin-1-ylmethyl, R_2 represents hydrogen or hydroxy, R_3 represents hydrogen, hydroxy or methyl, R_4 represents hydrogen or methyl, and R_5 represents hydrogen, chlorine or dimethylamino, antimalarial agents of the quinine type, and analogues having an 8-aminoquinoline, a 4-aminoquinoline, a 9-aminoacridine, a 1,3,5-triazine or pyrimidine structure, antischistosomatics in which the hydrophobic, non-polar group is optionally 6-chloro-,4-methyl- or 4-hydroxymethyl-substituted xanthonyl or thioxanthonyl, and the hydrophilic, polar group is diethylamino, antiviral agents of the cyclic amines type, and glucocorticoids that are esterified in the 21-position by an amino acid, or as carboxylic acid salts of the formula 2 having biological activity or carboxylic acids that can be converted into them by salt formation, salts of glucocorticoids that are esterified in the 21-position by a dicarboxylic acid, short-term narcotics of the 3,20-dioxo-5β-pregnane type that can be esterified by succinic acid, salts of

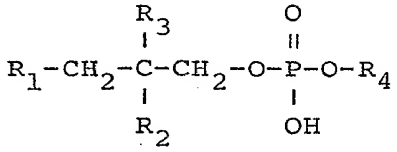
choleritics, analgesically active salts of substituted phenylacetic acids or 2-phenylpropionic acids, analgesically active anthranilic acid derivatives of the formula



(2.1)

in which R_1, R_2 and R_3, independently of one another, each represents hydrogen, methyl, chlorine or trifluoromethyl, analgesically active anilino-substituted nicotinic acid derivatives, analgesically active heteroarylacetic acids or 2-heteroarylpropionic acids having a 2-indol-3-yl or pyrrol-2-yl radical, analgesically active indenylacetic acids, analgesically active heteroaryloxyacetic acids, prostanoic acids that stimulate the smooth musculature, penicillanic acid and cephalosporanic acid derivatives having antibiotic action with 6β- or 7β-acylamino groups, which are present in fermentatively, semi-synthetically or totally synthetically obtainable 6β-acylamino-penicillanic acid or 7β-acylaminocephalosporanic acid derivatives or 7β-acylaminocephalosporanic acid derivatives modified in the 3-position, and other β-lactam antibiotics, antineoplastics having a 4-[bis-(2-chloroethyl)-aminophenyl]-butyric acid structure, or antineoplastics having two carboxy groups, or, as compounds of the formula 3, neurotransmitters in which

the hydrophobic group is methyl substituted by hydroxyphenyl, thyroid hormones having iodine-substituted phenyl radicals, or antineoplastics having an amino acid structure, or, as a compound of the formula 4, betamethasone disodium phosphate, dexamethasone disodium phosphate, cortisone phosphate, hydrocortisone phosphate, prednisolone disodium phosphate or paramethasone-21-disodium phosphate, or, as salt-type compounds having a hydrophobic group and a hydrophilic imidazoline, imidazolidine or hydrazino group, salts of anti-depressantly active hydrazine derivatives, for example α-sympathomimetics having an imidazoline structure, α-sympatholytics having an imidazoline structure, centrally active antihypertensives having an imidazoline structure, or vasodilatators having a hydrazino group, and (II), as the phospholipid, a compound of the formula



(5)

in which both radicals R_1 and R_2 represent alkyl, alkenyl, alkoxy, alkenyloxy or acyloxy each having from 10 to 20 carbon atoms, R_3 represents hydrogen or C_1-C_4-alkyl, and R_4 represents hydrogen, substituted C_1-C_7-alkyl, C_1-C_7-alkyl or a carbohydrate radical having from 5 to 12 carbon atoms, or a salt thereof.

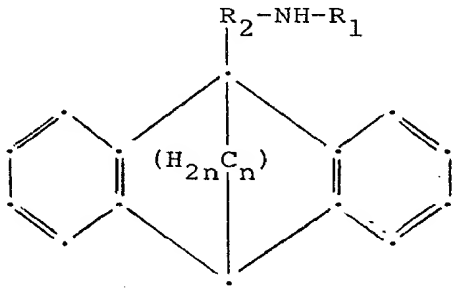
5. Process according to claim 4, characterised in

that there are homogeneously mixed and dispersed (I), as the substituted ammonium compound or as the corresponding amino compound that can be converted into the ammonium compound by salt formation, acetylcholine chloride, methacholine chloride, carbachol, muscarine, pilocarpine, arecoline, phyostigmine, neostigmine, pyridostigmine bromide, serotonin, histamine, tryptamine, bufotenine, psilocybin, morphine, hydromorphone, oxymorphone, levorphanol, codeine, hydrocodone, oxycodone, nalorphine, naloxone, naltrexon, buprenophine, butorphanol, nalbiphine, pholcodine, pentazocine, ketamine, metazocine, pentazocine, cyclazocine, pethidine, cetobemidon, alphaphrodine, ethoheptazine, prodilidine, profadol, methadone, normethadone, isomethadone, dipipanone, phenadoxone, dimephethanol, dextromoramide, D-propoxyphene, 1-benzyl-2-dimethylaminomethyl-1-propanoyloxytetralin, tramadol, dimethylthiambutene, diampromide, phenampromide, propiram, tilidine, metopholine, etonitazene, ergotamine, dihydroergotamine, dihydroergocryptine, methysergide, lisuride, dimetotiazin, dizotifen, oxetoron, cyproheptadine, procaine, chloroprocaine, hydroxyprocaine, propoxycaine, oxybuprocaine, propoxymetacaine, piridocaine, leucinocaine, butacaine, tetracaine, hydroxytetracaine, cornecaine, edan, piperocaine, cyclomethycaine, parethoxycaine, stadacain, cinchocaine, lidocaine, pyrrocaine, granocaine, butanilicaine, tolycaine, mepivacaine, bupivacaine, prilocaine, carticaine, dipiperidon, propicocaine, dyclonine, pramocaine, fomocaine, quinisocaine, profenamine, promethazine, periciazine, perimethazine, chlorpromazine, perphenazine, prochlorperazine, triflumpromazine, trifluoperazine, fluphenazine, thioridazine, mesoridazine, piperacetazine, acetophenazine, ethymemazine, di-

methacrine, opipramol, clomipramine, imipramine, desimipramine, trimipramine, chloroprothixene, thiothixene, amitriptyline, nortriptyline, doxepin, thiepin, protriptyline, prothipendyl, femoxetin, citalopram, zimelidine, trebenzomin, viloxazine, nomifensine, femoxetin, tranylcypromine, pargyline, etryptamine, flurazepam, mescaline, N_α,N_α-dimethyltryptamine, bufotenine, psilocin, psilocylein, scopolamine, atropine, benzatropin, trihexyphenidyl, cycrimine, pridinol, biperidin , procyclidine, caramiphen, phenglutarimide, orphenadrine, chlorphenoxamine, metixen, doxapram, amphetamine, methamphetamine, propylhexedrine, prolintane, fencamfamine, methylphenidol, pipradrol, phenmetrazine, diethylpropion, meclofenoxat, naftidrofuryl, dexamphetamine, phentermin, chlorphentermine, fenfluramine, amfepramone, phenmetrazine, phendimetrazine, tubocumarin, alcuronium chloride, gallamin triethiodide, hexacarbacholine bromide, pancuronium bromide, suxamethonium chloride, decamethonium bromide, scopolamine butyl bromide, bevonium methyl sulphate, valethamate bromide, methanteline bromide, camylofine, hexahydroadiphenine, adiphenine, fencarbamide, benzyclamine, ditaxol, chloroquine, tamoxifen, ethamoxytriphetol, phenbenzamine, tripelenamin, chlorpyramine, mepyramine, metaphenilene, metapyrilene, chloropyrilene, histpyrroclin, bamipin, thenalidine, clemizole, methdilazine, isothipendyl, oxomenazine, diphenhydramine, medrylamine, chlorophenoxamine, silachlorophenoxamin, carbinoxamine, diphenpyraline, clemastine, amethobenzepine, pheniramine, chlorophenamine, bromopheniramine, triprolidine, cycliramine, phenindamine, dimetindene, cyproheptadine, ketotifen, epinephrine (adrenaline), norepinephrine (noradrenaline), dopamine, nordefrin, ethylnorepinephrine, isoprenaline, iso-

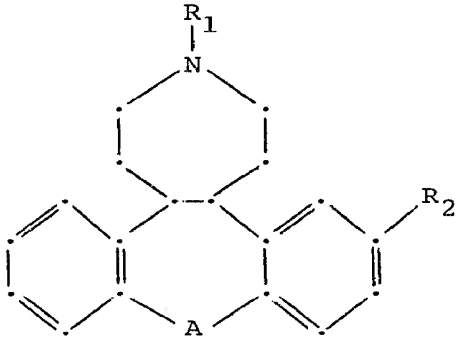
ethorine, metaproterenol, orciprenaline, metaraminol, phenylephrine, hydroxyamphetamine, methoxyphenamine, methoxamine, albuterol, ephedrine, norephedrine, fenfluramine, phenylpropanolamine, pholedrine, tyramine, dichloroisoprenaline, norfenefrine, octopamine, etilefrin, acebutolol, atenolol, metoprolol, toliprolol, alprenolol, oxprenolol, bunitrolol, bupranolol, talinolol, phenbutolol, bufetolol, varbian (R,S- or S-form), propanolol, indenolol, pindolol, mepindolol, nadolol, bunolol, sofalol, nifenalol, cabetalol, bufenalol, reserpine, rescinnamine, syringopine, chlorotetracycline, oxytetracycline, tetracycline, demethylchlorotetracycline, metacycline, doxycycline, minocycline, rolitetracycline, quinine, conquinidine, quinidine, cinchonine, pamaquine, primaquine, pentaquine, chloroquine, santoquine, hydroxychloroquine, amodiaquine, mepacrin, biguanid-1,3,5-triazin, proguanil, bromoguanil, chloroproguanil, nitroguanil, cycloguanilembonate, pyrimethamine, trimethoprim, lucanthone, hycanthone, miracil A or B, amantadine, cyclooctylamine, rimantadin, prednisolone diethylaminoacetate, and (II), as the phospholipid of the formula 5, natural lecithin (R_3 = hydrogen and R_4 = 2-trimethylammonium ethyl), natural cephalin (R_3 = hydrogen, R_4 = 2-ammonium ethyl) having different acyloxy radicals R_1 and R_2, synthetic lecithin or cephalin having different or identical acyloxy radicals R_1 and R_2, natural phosphatidyl serine (R_3 = hydrogen, R_4 = 2-amino-2-carboxyethyl) having different acyloxy radicals R_1 and R_2, synthetic phosphatidyl serine having different or identical acyloxy radicals R_1 and R_2, or natural phosphatidic acid (R_3 and R_4 = hydrogen having different acyloxy radicals R_1 and R_2).

6. Process according to claim 4, characterised in that there are homogeneously mixed and dispersed, as the substituted ammonium compound or as the corresponding amino compound that can be converted into the ammonium compound by salt formation, a compound selected from the group of the acid addition salts of antidepressants of the formula



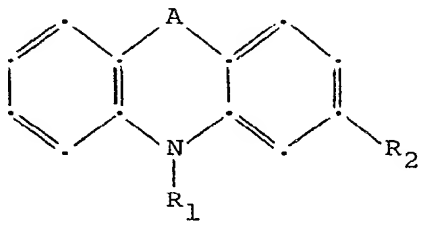
(1.8)

in which R_1 represents lower alkyl, for example methyl, R_2 represents lower alkylene or hydroxy-lower alkylene, and n represents 0 or 2, acid addition salts of antidepressants of the formula



(1.9)

in which R_1 represents lower alkyl, A represents the group $N-\!\!>R_1$, oxygen or sulphur, and R_2 represents hydrogen or cyano, acid addition salts of anti-depressants of the formula



(1.10)

in which R_1 represents lower alkylamino-lower alkyl, di-lower alkylamino-lower alkyl or 3-(4-(2-hydroxy-ethyl)-piperazin-1-yl)-n-propyl and A represents ethylene or vinylene, or acid addition salts of amphetamine, methamphetamine, benzphetamine, propyl-hexedrine, prolintan, fencamfin, methylphenidate, pipradrol, phenmetrazine, adiphenine, epinephrine, norepinephrine, dopamine, nordefrin, ethyl-norepinephrine, isoprenaline, isoethorine, meta-proterenol, orciprenaline, metaraminol, phenylephrine, hydroxyamphetamine, methoxyphenamine, ephedrine, norephedrine, pholedrine, tyramine, norfenefrin, octopamine, acebutolol, atenolol, toliprolol, alprenolol, oxprenolol, bunitrolol, bupranolol, talinolol, phenbutolol, bufetolol, varbian (R,S-form and S-form), reserpine, rescinnamine, syringopine or prednisolone diethylaminoacetate, and (II), as the phospholipid of the formula 5, natural lecithin or cephalin, synthetic 1-palmitoyl-2-oleoyl lecithin or cephalin, dipalmitoyl, distearoyl, diarachinoyl, dioleoyl, dilinoyl or dilinoleyl lecithin or cephalin, natural phosphatidyl serine, synthetic 1-palmitoyl-2-

oleoylphosphatidyl serine, dimyristoyl- or dipalmitoyl-phosphatidyl serine, or natural phosphatidic acid.

7. Process according to claim 4, characterised in that there are homogeneously mixed and dispersed, as the substituted ammonium compound of the formula 1 or as the corresponding amino compound that can be converted into the ammonium compound by salt formation, 1-(2R-2-hydroxy-3-methylaminopropyl)dibenzo[b,e]bicyclo[2.2.2]octadiene, and the 2R,S-isomeric mixture, maprotiline, benzoctamine, 3-methyldibenzo[2,3:6,7]-oxepino[4,5-d]azepine hydrochloride, 7-cyano-3-methyl-2,3,4,5-tetrahydro-1H-dibenzo[2,3:6,7]-thiepino[4,5-d]azepine methanesulphonate, 3,10-dimethyl-1,2,3,4,5,10-hexahydrodibenzo[b,f]azepino[4,5]azepine maleate, clomipramine, opipramol, desipramine, imipramine or imipramine N-oxide, ephedrine, norephedrine, 1-isopropylamino-3-[4-(2-methylthioethoxy)-phenoxy]-propan-2-ol, 1-isopropylamino-3-(2-pyrrol-1-ylphenoxy)-propan-2-ol, oxprenolol, prenalterol, adiphenine, prednisolone diethylaminoacetate, or reserpine, and (II), as the phospholipid of the formula 5, natural lecithin or cephalin, synthetic 1-palmitoyl-2-oleoyl lecithin or cephalin, dipalmitoyl, distearoyl, diarachinoyl, dioleoyl, dilinoyl or dilinoleyl lecithin or cephalin, natural phosphatidyl serine, synthetic 1-palmitoyl-2-oleoylphosphatidyl serine, dimyristoyl- or dipalmitoyl-phosphatidyl serine or natural phosphatidic acid.

8. Process according to claim 4, characterised in that there are homogeneously mixed and dispersed, as the carboxylic acid salt or the carboxylic acid compound that can be converted into the carboxylic acid salt by salt formation, methylprednisolone sodium succinate, prednisolone sodium succinate, 3,20-dioxo-5β-

pregnane, hydroxydione succinate sodium, 11,20-dioxo-3α-hydroxy-5α-pregnane, alphadolon, a cholic acid or deoxycholic acid salt, alclofenac, ibufenac, ibuprofen, clindanac, fenclorac, ketoprofen, fenoprofen, indoprofen, fenclofenac, diclofenac, flurbiprofen, pirprofen, naproxan, benoxaprofen, carprofen, cicloprofen, mefenamic acid, flufenamic acid, tolfenamic acid, meclofenamic acid, milflumic acid, clonixin, flunixin, indometacin, oxmetacin, intrazol, acemetazin, cinmetacin, zomepirac, tolmetin, colpirac, tiaprofenic acid, benzadac, PGE_2 (dinoprostone), $PGF_{2\alpha}$ (dinoprost), 15 (S)-15-methyl-PGE_2, 15 (S)-15-methyl-$PGF_{2\alpha}$(carboprost), (±)15 (Xi)-15-methyl-13,14-dihydro-11-deoxy-PGE_1 (deprostil), 15 (S)-15-methyl-11-deoxy-PGE_1 (doxaprost), 16,16-dimethyl-PGE_2, 17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$, 16-phenoxy-17,18,19,20-tetranor-$PGF_{2\alpha}$ or N-methylsulphonyl-16-phenoxy-17,18,19,20-tetranor-$PGF_{2\alpha}$(sulproston), nalixidic acid, cinoxacin, oxolinic acid, pironidic acid, pipenidic acid, penicillin G or V, phenethicillin, propicillin, nafcillin, oxacillin, cloxacillin, dicloxacillin, flucloxacillin, cyclacillin, epicillin, mecillinam, methicillin, azlocillin, sulbenicillin, ticarcillin, mezlocillin, piperacillin, carindacillin, azidocillin, ciclazillin, cefaclor, cefuroxime, cefazlur, cephacetrile, cefazolin, cephalexin, cefadroxil, cephaloglycin, cefoxitin, cephaloridine, cephsulodin, cefotiam, ceftazidine, cefonicid, cefotaxime, cefmenoxime, ceftizoxime, cephalothin, cephradine, cefamandol, cephanone, cephapirin, cefroxadin, cefatrizine, cefazedone, ceftrixon, ceforanid, moxalactam, clavulanic acid, nocardicine A, sulbactam, aztreonam, thienamycin, chlorambucil or methotrexate, and, (II), as the phospholipid of the formula 5, natural lecithin or cephalin, synthetic 1-

palmitoyl-2-oleoyl lecithin or cephalin, dipalmitoyl, distearoyl, diarachinoyl, dioleoyl, dilinoyl or dilinoleyl lecithin or cephalin, natural phosphatidyl serine, synthetic 1-palmitoyl-2-oleoylphosphatidyl serine, dimyristoyl- or dipalmitoyl-phosphatidyl serine or natural phosphatidic acid.

9. Process according to claim 8, characterised in that there are homogeneously mixed and dispersed, as the carboxylic acid salt or the carboxylic acid that can be converted into the carboxylic acid salt by salt formation, the sodium salts of diclofenac and pirprofen, and (II), as the phospholipid of the formula 5, natural lecithin or cephalin, synthetic 1-palmitoyl-2-oleoyl lecithin or cephalin, dipalmitoyl, distearoyl, diarachinoyl, dioleoyl, dilinoyl or dilinoleyl lecithin or cephalin, natural phosphatidyl serine, synthetic 1-palmitoyl-2-oleoylphosphatidyl serine, dimyristoyl- or dipalmitoyl-phosphatidyl serine or natural phosphatidic acid.

10. Process according to claim 1, characterised in that the homogeneous mixture is prepared by lyophilisate or film formation.

11. A pharmaceutical composition comprising an aqueous dispersion wherein the dispersed phase contains a pharmaceutically active substance encapsulated within a unilamellar liposome prepared according to the process of claim 1.

12. A pharmaceutical composition comprising an aqueous dispersion wherein the dispersed phase contains a pharmaceutically active substance encapsulated within a unilamellar liposome prepared according to the process of claim 1 and pharmaceutically acceptable carriers.

FETHERSTONHAUGH & CO.
PATENT AGENTS

OTTAWA, CANADA

SUBSTITUTE

REMPLACEMENT

SECTION is not Present

Cette Section est Absente